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APHASIA*

BY

SIR CHARLES SYMONDS

It seems nowadays to be the fashion in discussing aphasia to begin with the consideration of speech as a psychological function and to proceed to the analysis and classification of the dysphasias in terms of disordered thinking, with little concern for the problems of anatomy and physiology that must be involved when a disorder of speech results from local disease of the brain. This represents a swing of the pendulum away from the method of the older writers on this subject, who sought on the basis of clinical and pathological observation to classify the dysphasias in terms of the situation of the lesion and its interference with hypothetical centres and pathways serving the different functions involved. In those days the observation of a new type of dysphasia required some rearrangement of the plan of centres and pathways, which became more and more complicated and less and less satisfactory. Henry Head (1920), impatient of the diagram makers, swept their work aside and attempted a new classification of the dysphasias in psychological terms. In so doing he asserted that there was no such thing as an isolated affection of one part of the speech function. This struck at the foundations of all previous theory for which the occurrence of " pure " aphasias—word blindness, word deafness, pure motor aphasia, and agraphia—was essential. Head stated that in particular cases certain aspects of speech function might be disturbed more than others, but the function of speech was always disturbed as a whole. In one sense he was right, for the function of a whole must always depend to some extent upon that of its parts, but in another sense I believe he was wrong. His intentness on his own theories led him to ignore certain facts of clinical observation.

It is true that the disorders of speech function can be described only in psychological terms, but if we repeatedly observe in disease a specific disorder of speech function the occurrence entitles us to conclude that there are separate anatomical arrangements, or one might equally well call them neurophysiological dispositions, subserving the psychological function affected. This, I think, was what the more thoughtful of the earlier writers on aphasia meant when they used the word " centre ", though this term later became debased and has gone out of fashion. Jackson usually spoke of anatomical substrata. Neurophysiological disposition is perhaps better now that we think more in terms of circuits than areas.

If we examine the clinical facts impartially we shall find, I submit, abundant evidence of the localization of function in this sense. It is important, however, to begin with a clear idea of what we mean by the function of speech. As I understand it, this includes all psychological processes involving the use of language, including the understanding of speech both spoken and written, the expression of speech in both forms, and the use of words in thinking. The understanding and expressive use of figures and musical notes are so closely allied to the function of speech that they should also be considered in any discussion of aphasia. I have said that for the conclusion that there is localization of function in the sense used there must be repeated observation of particular disorder. We should not expect these specific disorders of function to be at all common, for cerebral disease is rarely so circumscribed or selective as to be capable of producing such effects.

There are, however, to be found numerous examples of speech disorder so distinct from one another that they must depend upon the loss by disease of separate anatomical arrangements. Of these the best known is the condition first described by Déjerine (1892) as pure word blindness. Many instances have since been recorded and the subject has recently been reviewed by Holmes (1950), with the addition of an excellent case. The essential features are, as the name implies, inability to read, with preservation of understanding of the spoken word, and the ability to name objects, speak, and

* A lecture given at the National Hospital, Queen Square, London.

write. I have myself seen several such cases, and it is indeed remarkable to meet a person whose intelligence is unimpaired, whose powers of conversation are entirely normal, who is able to write letters or essays without the least difficulty, but is unable to read a word of what he has written. These cases, however, differ in small respects from one another. In most of the recorded cases the ability to read music has been lost when it was previously possessed, but Hinshelwood (1900) and others since have reported examples in which this ability was preserved, although words could not be read. In nearly all cases the ability to read numerals is preserved, together with the power of calculation. In such cases, as I have myself observed, Roman numerals have no meaning for the patient. He reads them, if at all, as letters.

Even within the clinical syndrome of pure word blindness, therefore, there are to be found refinements of symptomatology which must surely depend upon equivalent refinements of structural organization. To support this conclusion there are cases in which the patient can read words, but not figures, and there is a case recorded by Proust (1872) of a patient, previously an accomplished musician, who without any reading disability in the ordinary sense, after what was presumably a vascular lesion, could still compose and write musical notes, though he was quite unable to read them—the musical counterpart of pure word blindness.

These observations indicate the existence of separate neurophysiological dispositions or anatomical arrangements for the functions concerned, without so far pointing to any well defined situation of the lesion, and precise definition has so far proved impossible. Nevertheless there are clues which have important localizing value. In nearly all the recorded cases of pure word blindness there has been right homonymous hemianopia : in none has there been any sensory impairment or spatial disorientation. There is abundant evidence from cases of gunshot wounds of the occipital cortex to show that a patient with hemianopia from a lesion in this situation does not have word blindness. The lesion responsible for pure word blindness, therefore, presumably involves the optic radiation before it reaches the striate cortex and after it has left the parietal lobe. It has been argued by Déjerine (1892), Bastian (1898), and others that afferent pathways from the right occipital lobe crossing in the corpus callosum must be involved to account for word blindness in the whole of both visual fields, and this seems a reasonable assumption.

The patient with word blindness of the type we have been discussing can neither read to himself nor aloud. There is, however, a much rarer form of word blindness in which reading aloud is possible but there is no comprehension of what is read. Wilson (1926) remarks of such a case :

> " The patient can read aloud in a mechanical way and be at the same time ignorant or oblivious of the meaning of what he reads—exactly as a person of sufficient education can pronounce and read a foreign language from the text while every particle of meaning is hid from him."

Such a patient, as Wilson says, is suffering from word-meaning-blindness, not from word-sight-blindness. This state of affairs, however, can surely only exist when there is also word deafness, or the patient reading aloud would hear and understand the words as he said them. I suppose this to be so and have only met with word-meaning blindness in association with word deafness. In one such case, to which I shall refer later, the power of reading figures was unimpaired, the patient was able to calculate with ease and kept his own accounts. But he could not appreciate the significance of Roman numerals. Given XVII he read out " Ex-vee-one-one " though 17 was read aloud accurately and understood. Nor could he interpret the signs for multiplication, subtraction and so on, but if the figures were arranged for him in such a way that he could understand what was required of him without the conventional signs his calculations were prompt and accurate.

Pure word deafness is much rarer than pure word blindness, probably because the anatomical arrangements concerned are packed into a region which has many other functions. There are nevertheless many well authenticated examples. One of the most recent is that reported by Hemphill and Stengel (1940), a traumatic case in a labourer aged 34. The head injury was due to a fall, and there was a fissured fracture of the left squamous temporal bone with a post-traumatic amnesia of three or four days. When recovered from the traumatic confusion the patient was thought to be deaf, but this was disproved by audiometry and clinical observation. The main facts about this patient are as follows. He talked fluently without paraphasia or grammatical error, and the same was true of his writing. He could read correctly and understand what he read. His intellectual functions were normal for his educational background and social status. He was, however, almost totally unable to comprehend the spoken word. The case report is of particular value in that it includes the patient's running commentary upon his own disability. For example, asked, " What is your name ?", his response was, " Voice comes but no words. I can

hear, sound comes but words don't separate." Asked again, " How are you ?" " That is letters what you are saying." Told, " Show your tongue ". Response, " I can't get it. I can hear your voice coming, but it does not finish. Your voice is dead plain." Summarizing his own experience, he said, " I can hear you dead plain, but I cannot get what you say. The noises are not quite natural. I hear your voice, but not the words. I can hear but not understand. It does not pronounce itself." This is as good an example as any in the literature of word-sound-deafness in a pure form, comparable in almost every respect with pure word blindness. Here we have again a defect of function so circumscribed that it must have localizing value. What anatomical evidence exists in such cases points to the middle part of the left superior temporal gyrus, adjacent to the auditory cortex, as the site of the lesion.

Of even rarer occurrence than word-sound-deafness is word-meaning-deafness. Here the patient can repeat the words he hears without understanding their meaning. This I have not observed except in association with some other disturbance of speech function, nor can I find any clear account in the literature of pure word-meaning-deafness, though Wilson seems to imply that he has seen it. It has usually been observed after partial recovery from a more general kind of dysphasia as in Byrom Bramwell's case (1897) of a young woman who had a sudden cerebral attack after a confinement, resulting in a gross disorder of speech function both on the expressive and the receptive sides, but more severe on the latter. She made a rapid recovery in other respects but was left with a severe impairment of understanding the spoken word. Her condition is thus summarized by Byrom Bramwell. The patient could repeat correctly words and sentences which she could not understand when spoken, and could write from dictation long sentences which she was quite unable to understand by the ear, though she was able to read and understand what she had written. At this time there appears to have been no impairment of speech function on the outgoing side, nor any difficulty in reading, but there was some difficulty in naming objects.

This last defect, that of naming objects, appears to have been present in all the cases of word-meaning-deafness so far recorded, as it was in the only case I have had the opportunity of studying in detail. This was of exceptional interest in that the patient suffered from both word-meaning-deafness and word-meaning-blindness, and apart from these defects and the inability to name objects showed little other disturbance of speech function. The patient was a man aged 50 on his first admission to hospital, previously of good intelligence and Deputy Clerk of Works at the Bank of England, who had for two years shown symptoms of an insidiously progressive dementia, probably due to Pick's disease, though he is still living and the diagnosis has therefore not been established. He had been at his work until the date of his admission, evidence that at that time the dementia was not far advanced. His chief disability at that time was difficulty in understanding what was said to him. To this later was added an equal difficulty in understanding what he read and a particular difficulty in naming objects.

I have records of many conversations with this patient, conducted, of course, with great difficulty and with the aid of pantomime, and shall try to convey to you by means of an extract the nature of his speech disorder. In spontaneous speech he was quite eloquent within the limitations of his confined interests and imperfect memory. He would talk at length about his past experiences and especially of his work at the Bank. He was equally fluent in writing of these experiences. He could also, when he understood what was required of him, give an accurate account either in speech or writing of a day in the ward. In conversation and writing as a rule he formed his words and sentences correctly, and pronunciation and intonation were normal. Only very occasionally did he use wrong or mutilated words. He was able to repeat words and sentences correctly, wrote correctly to dictation, copied letters and words in capitals or script and transcribed from script to capitals or vice versa quickly and accurately, and could read aloud without difficulty, though with occasional mispronunciation. But he could understand little of what he heard or read.

Here is a record of part of one of our interviews. His pronunciation was correct unless otherwise indicated. My questions were verbal except those in italics which were written.

Question. What are your initials ?	Response. What's initials ? (correctly pronounced).
Q. *Initials.*	R. In - it - eye - als. What's that ?
Q. *Initials.*	R. In - it - eye - als. Don't know what that is though.
Q. *Your initials are C. L.*	R. Your in - it - eye - als are C. L. C. L. that's me. Charles Leale.
Q. Your initials are C. L.	R. I don't know that.
Q. What is your Christian name ?	R. I don't know what Christian is.

Q. Your surname is Leale?	R. Yes, L - E - A - L - E.
Q. What is your surname?	R. My surname—Charles Frederick Leale—is that what you mean?
Q. Your Christian name is what?	R. What's Christian mean? I don't know that word.
Q. Your surname is what?	R. What is the word surname? My name?
Q. What is your name?	R. My name! Charles Frederick Leale.
Q. What is your Christian name?	R. My name? Leale do you mean?
Q. *Surname is Leale.*	R. (Read aloud correctly). Adds, Is that my time you've got at the top, 50? I'm not 50. I'm 53. (This reference was to his age written on the sheet of paper I was using. It was stated as 50, his age when first admitted three years previously.)
Q. *Christian names are Charles Frederick.*	R. (Read aloud correctly).
Q. What are your Christian names?	R. What is Christian name? Christianity comes throughout the world.
Q. What is your surname?	R. Don't know that, surname, what's surname?
Q. *What is your surname?*	R. (Read aloud correctly).
Q. Yes?	R. (Re-reads correctly). Is that my name?
Q. What *is* your surname?	R. What is surname?
Q. *Your surname is Leale.*	R. (Read aloud correctly).
Q. What is your surname?	R. What is surname?
Q. What is your name?	R. My name is Leale (promptly and in a tone which implies of course).
Q. What are your other names?	R. My wife's name? My boy is married.
Q. What are your names besides Leale?	R. What's names? What?
Q. What are your names besides Leale?	R. What's "sides"? My boy's and girl's names?
Q. Are you Harry Leale?	R. What's Harry?
Q. Are you George?	R. What's George?
Q. *Are you George Leale?*	R. (Read aloud correctly).
Q. Are you Charles Frederick Leale?	R. I'm Charles Frederick Leale—Yes (again tone implies of course).
Q. Who am I?	R. What? What's your name? You are Sir Charles aren't you? I forget.

That his difficulty was essentially that of understanding speech could be shown in a variety of ways. For example, he had no difficulty in understanding and reading figures and was able to do quite complicated sums. He showed, however, the inability to appreciate Roman numerals which is characteristic of word blindness. When a collection of coins and notes was placed before him he had no difficulty in identifying them to request, provided that the wording was numerical. If the significance of the request depended upon words it was usually missed. Asked to show a two and sixpence, he did so promptly: asked to show a half-crown, he simply said, "What's half-crown—I don't know". Asked to show a pound, he would look puzzled, and would sometimes, but not always, succeed. Asked to show the quid, he said, "Eh? What's a quid?" His response to written instruction was similar. When I wrote "Show me the 10s." he read it aloud and at once did so. When I next wrote "Show me the ten bob" he read it aloud correctly and then said "Show me the ten bob—what's bob?"

One of the most interesting features of his condition was his ability to use in expressing his own thoughts words which had no meaning for him when I said or wrote them. For example, I got him after some difficulty with repetition, gesture, and pantomime to answer the question, "What was your work?" and he replied, "I was an expert in the building trade." I then said, "What is trade?", and his response was, "Trade? What's trade? What is that word? I don't know." He could do no better when I wrote the question. In this respect his behaviour was so odd that anyone examining him for the first time might have thought he was play-acting, but throughout many interviews the disorder of speech remained quite consistent. It was evident that he was indeed suffering from word-meaning-deafness and word-meaning-blindness with relatively little impairment of the ability to express his own thoughts in speech or writing. The disorder was almost wholly on the receptive side, though he had, as I have already said, the inability to name objects whose use he could readily demonstrate.

I do not suppose it to be possible to define the situation of the lesion responsible for this man's symptoms in anatomical terms or to interpret the disorder of function in terms of physiology. The disorder is psychological, but its occurrence as a well defined symptom complex from organic disease implies disorganization of specific anatomical arrangements.

So far I have dealt with the receptive aspects of

speech function. I agree with Wilson (1926) that this is a better term than sensory, which has a physiological meaning and is inappropriate for the description of psychological disorder. On the expressive side there is also evidence of localization of function. There is no doubt of the occasional occurrence, from vascular lesion or localized injury, of dumbness or mutism without impairment of comprehension of the spoken or written word, and without any defect of writing. This was the clinical picture first described by Broca in association with a lesion at the posterior end of the inferior frontal gyrus, and this localization has been proved true in other cases. For some years I had a woman under my care at this hospital who awoke one morning bereft of speech, but at no time had any difficulty in expressing herself in writing. This method, however, she found too cumbersome for conversation, and she therefore trained her sister to act as interpreter. She would trace with her forefinger letters on the back of her sister's hand, and the latter would speak for her. Quick to understand what she heard and read and eager to express herself to me, this alert old lady has left a lasting impression on my mind. She never spoke again, died later as far as I recollect from a lesion in the other hemisphere, and proved to have a small area of softening in the appropriate situation on the left.

Most of these patients show some degree of recovery, and it is then possible, as Bastian (1898) first observed, to distinguish between two kinds of expressive disorder. In one a few words first return, " Yes ", " No ", or expletives, or a phrase or two, and are correctly pronounced, but often inappropriately used. In response to stimulation the patient's lips either form these words or are motionless. In the other variety recovery begins with attempts at articulation, which as soon as they begin to be audible can be recognized as appropriate and grammatical expressions of thought. This condition Bastian called " aphemia," and it is unfortunate that the name has not been kept for it. I have seen several examples, and in each instance there has been so complete a paralysis of the face on the opposite side to the cerebral lesion as to suggest a lower neuron affection. This may be limited to voluntary movement, as in the case of a woman I saw who showed no movement either of the upper or lower half of the right face on request, though the left half moved normally. When, however, she wept facial movement was symmetrical. She had been found in the early morning mute and in a state of extreme agitation, and was thought to be suffering from a state of agitated depression. The dissociated facial weakness was interpreted as hysterical. When I gave her pencil and paper the expression of relief in her eyes and the eagerness and fluency with which she wrote an account of her disability were dramatic. Bastian proposed an anatomico-physiological distinction between what he called " motor aphasia " and aphemia as follows. In motor aphasia he thought the area for kinaesthetic images of words was destroyed, in aphemia the descending fibres from this area going with the pyramidal fibres to the lower motor neurons for the muscles of articulation. Hence, he argued, the complete escape in aphemia, even in the stage of mutism, of intellectual function. In motor aphasia, on the other hand, the loss of kinaesthetic images might, and, he supposed, did, interfere with thought, which may be formulated to some extent by the revival of kinaesthetic images—silent speech. It is true, so far as my own observations go, that the patient with motor aphasia does in the early stages show confusion, while the aphemic does not.

I have recently had a patient with aphemia under my care, whom I persuaded, after he had been mute for several days, first to intone the vowels, and then to sing with me the first words of " Three blind mice ". He thereupon wrote, " The secret of this is that in singing preoccupation with the melody seems to remove some kind of inhibition. It reminds me of Dr. Johnson's remark that things too silly to be said may yet be sung ". He clearly had no disorder of thought or its expression in words.

Pure agraphia I have never seen, nor read a satisfactory account of a case, though there are several on record in which writing has been much more severely affected than speech. If there are separate anatomical arrangements for writing, as there well may be, they are probably so closely intertwined with those for the more general use of the hand that paralysis hides the agraphia.

The examples I have taken to illustrate the localization of speech function have been of the simplest kind. The disorders of speech usually encountered are complex and involve both reception and expression, though the one may be much more severely involved than the other. These more complex speech disorders can and should be studied with the object of analysis and classification, and it is in this field that Head in particular advanced so far, though his classifications have never been widely accepted and have contributed little of practical value for the clinician. But unless classifications are established the opportunities occasionally offered by disease for the localization of function will be missed, and, as I have already stated, if a special type of speech disorder can be

isolated by clinical observation and subsequently recognized, this affords proof that there are special parts of the brain concerned with this function even though we do not know at present exactly where they are. The simplest or " pure " types of aphasia provide the best starting point for the advance of knowledge, which has been hindered by the extreme rarity of such cases.

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THE EFFECTS OF METHEDRINE AND OF LYSERGIC ACID DIETHYLAMIDE ON MENTAL PROCESSES AND ON THE BLOOD ADRENALINE LEVEL

BY

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The psychological effects of drugs and their applications in psychiatry are of theoretical as well as practical interest, but their study has rarely penetrated beyond a description of symptoms and little is known of their mechanisms of action. Since a method for the estimation of adrenergic amines in blood has recently been developed (Weil-Malherbe and Bone, 1952) we decided to study the changes of blood adrenaline levels during drug action and to correlate them with mental changes. In this communication we report on results obtained with d-N-methylamphetamine hydrochloride ("methedrine") and lysergic acid diethylamide (L.S.D.).

The application of methedrine in psychiatry has been investigated by Levine, Rinkel, and Greenblatt (1948), Delay (1949), Rudolf (1949), Hope, Callaway, and Sands (1951) and Hoch, Cattell, and Pennes (1952b). In schizophrenic patients the drug is claimed to produce an increase of accessibility, emotional discharge, and verbalization of repressed or delusional material. Delay (1949), on the other hand, states that catatonic features, if present, are accentuated.

The psychological effects of L.S.D. in normal and psychotic subjects were first described by Stoll (1947) and his results were subsequently confirmed by Condrau (1949), Becker (1949), and Fischer, Georgi, and Weber (1951). DeShon, Rinkel, and Solomon (1952) studied the effects of L.S.D. on normal subjects and Busch and Johnson (1950), Forrer and Goldner (1951), and Hoch and others (1952a) similarly investigated its effects on psychotics. De Giacomo (1951) drew attention to the capacity of L.S.D., given in large doses by mouth, of producing symptoms of catatonia in schizophrenic patients, an effect resembling the action of bulbocapnine. Others have commented on the analogy with the action of mescaline.

Though the various authors tended to stress different symptoms as the chief characteristic of L.S.D. action, all are agreed as to its potency, for as little as 10 μg. by mouth has been sufficient to produce results. Psychotic patients, however, seem to be less sensitive and to require larger doses. When L.S.D. is taken by mouth symptoms appear within half an hour, reach their maximum in about two and a half hours, and gradually pass off in the following four to five hours. Occasionally mild after-effects are noted over the next few days.

The subjective complaints after a dose of L.S.D. are chiefly of headache, malaise, giddiness, nausea, feeling cold, anorexia, and palpitations. Objectively the examination of the autonomic and central nervous system is equivocal. On the other hand, psychological changes are prominent. Thought and speech may exhibit retardation, acceleration, blocking, and hesitancy; the speech may be slurred. The effect is one of euphoria, but depression as well as apprehension and depersonalization may occur. Disturbances of perception are common, especially in the visual sphere, as manifested by distortion, wrong perspective, or incorrect estimation of distances; colour perception may be poor or faulty. These effects increase with larger doses and may result in hallucinations. In the behavourial field under-activity with lack of initiative is most frequently observed, but restlessness and even agitation is sometimes noted. Unmotivated smiling and forced laughing have been described.

Busch and Johnson (1950) have drawn attention to the possible use of L.S.D. as an aid to psychotherapy since they found that psychotic patients responded with an increased production and verbalization of psychopathological material.

EXPERIMENTAL

Previous investigators gave L.S.D. by mouth. We, too, have used this route of administration in preliminary

experiments, but later the drug was given by intravenous injection. This procedure, being independent of the individual variations in intestinal absorption, had the advantage of producing a more standardized and less protracted time curve of effects; moreover the comparison with the effects of methedrine, which was also administered by intravenous injection, was facilitated. Forrer and Goldner (1951) found that L.S.D., when taken by mouth, is not toxic up to doses of 6 μg./kg. It was felt therefore that the intravenous injection would not involve undue risks. Initially small doses in the order of 25 μg. in 10 ml. of normal saline were used, but since these proved safe, the dose was eventually stepped up to 60 μg. dissolved in 5 ml. of normal saline. A stock solution of 1 mg. in 5 ml. saline was prepared and stored in the frozen state for not more than one week. It was further diluted immediately before use. Methedrine was employed in doses of 40 to 60 mg.

The subjects were investigated in the forenoon after an overnight fast. They were under constant observation in a quiet room and their psychological and neurological symptoms were noted. They were encouraged to lie down, but this was not insisted upon and they were allowed to move freely if they wished. Blood samples were withdrawn from the cubital veins before the injection and at five, 10, 20, 30, 40, 60, and 90 minutes after the injection. In three patients who were examined after oral administration of 40 μg. L.S.D. blood samples were withdrawn before ingestion and 0·5, 1, 1·5, 2, 2·5, 3, and 3·5 hours after ingestion. Blood sugar was estimated in duplicate on 0·2 ml. samples of whole blood by the method of Nelson (1944) after $Ba(OH)_2$–$ZnSO_4$ deproteinization. Adrenaline was determined on a sample of plasma according to Weil-Malherbe and Bone (1952).

Ten cases were investigated after the intravenous injection of L.S.D. and 11 after the injection of methedrine. Further patients who had been similarly treated are not included because of differing dosage or incomplete investigation. The two groups consist of an approximately equal number of male and female patients varying in age from 22 to 61 years. Four cases received both drugs in separate experiments. The diagnostic composition of the two groups is shown in Table I.

TABLE I
SURVEY OF CASES INVESTIGATED

Diagnosis	Number of Cases	
	L.S.D.	Methedrine
Depression	3	0
Paranoid schizophrenia	2	2
Other forms of schizophrenia	4	5
Anxiety hysteria	0	2
Psychopathic states	1	2

RESULTS

Symptomatology

L.S.D.—The intravenous injection of L.S.D. produced a train of events occurring at a relatively constant time interval. After five minutes a flushing of the face was observed in five patients and seven patients appeared more relaxed and at ease. Some spontaneously commented on this with remarks such as, "I feel I can concentrate better", "I look at you relaxed". Talkative patients became calmer.

After 10 minutes mental symptoms became noticeable, chiefly in the sphere of thinking, speaking, and behaviour. While depressed patients became more retarded in both movement and speech, cataleptic phenomena were noted in some non-paranoid schizophrenics. Blocking, incoherence, perseveration, echolalia, poor production of material occurred in all six schizophrenics in various combinations, and in one of them the pupils became unequal and eccentric but reacted to light and convergence. After 15 to 20 minutes changes in mood and affect appeared. The mood fluctuated between euphoria, excitement, and depression. In the euphoric phase the subject may laugh happily, make erotic advances, propose marriage, and behave flippantly. The swing-over to depression may take place rapidly and may be associated with crying, expressions of guilt, and occasionally the onset of abreaction; this may be followed, equally abruptly, by a swing of mood in the other direction. It is during this period that repressed material or new delusional thought contents may be produced. The emotions are appropriate to the thought content. These rapid mood swings were observed in all schizophrenic and psychopathic cases and persisted for two to three hours. Depressive patients, however, showed a steadily enhancing gloom and an accentuation of ideas of unworthiness and of mental retardation.

Changes in autonomic functions were observed in five cases after about 30 to 40 minutes. They consisted in subjective and objective shivering associated with goose-flesh and piloerection on the forearms in the case of men.

In six of the cases a change in the mental picture occurred after about 40 minutes. Apprehension and tenseness increased, sometimes progressing to agitation. Others showed an increase of mannerisms and grimaces. Only two schizophrenic patients gave at this time evidence of visual and auditory hallucinations. They appeared frightened and were completely inaccessible. This relatively rare occurrence of hallucinations is in striking contrast to the experience of most other observers who gave the drug by mouth. Four other patients became increasingly restless and agitated and one retarded depressive woman screamed

continuously for two hours. The patients seemed to feel an unexplainable sense of terror, clinging to the examiner and begging not to be left.

The symptoms gradually disappeared in the course of two to three hours. Occasionally a vague euphoria persisted for another day, but usually the effects of the injection had worn off by the afternoon.

Perception of external objects was in no way impaired. Size, distance, shape, and colour were accurately assessed. In none of our patients did depersonalization or derealization occur. This may have been due to the severe impairment of speech and inability of communicating, for we have noted that patients have looked at their arms and legs in a vague perplexed way, but direct questioning elicited no further information except in one patient who said, " I can't believe they are mine ". Another complained that his body felt lanky and loose at the joints. Neurological examination revealed no abnormality and E.E.G. records were normal.

Methedrine.—The effects of methedrine are perhaps better known. The effects of a 60 mg.-dose of methedrine resembled in many ways those of a 60 μg.-dose of L.S.D., and this similarity was particularly obvious in those patients who received both drugs.

As with L.S.D. the initial feeling is one of relaxation, starting sometimes with a swimming or floating sensation or with a transient pounding in the head. At this stage one mild-mannered, quiet-spoken schizophrenic patient burst out swearing in a loud voice for about a minute and then said, " I feel marvellous now. Why isn't it like this all the time? ". However, within five minutes he was speaking rapidly and incoherently and soon was maintaining any bizarre postures into which he was placed. He produced repressed material, but his speech became progressively slower and he became finally mute.

The appearance of cataleptic phenomena in varying degrees and for varying lengths of time was the rule for schizophrenic patients and was more marked than with L.S.D. Their speech may be incoherent, fragmentary, or delivered in telegraphic style, while blocking may occur in others.

The non-schizophrenic group exhibited pressure of talk which was always logical and often led to abreaction with resurrection of repressed material and much weeping and anguish ; this often resulted in a certain amount of relief and release from tension.

Mood fluctuations were not so prominent as after the injection of L.S.D. ; on the other hand, the mood often appeared to be incongruous, at least in the schizophrenic patients. They looked as if they were in absolute torment, but stated, " It is beautiful ", or claimed to be in heaven. Generally the previous disposition of mood was retained or even accentuated during the experiment.

Objective evidence of hallucinations was present in every case of schizophrenia. One clinically recovered patient became acutely schizophrenic for the space of two hours. Ten minutes after the injection he started to mumble to himself, struck postures, and was completely inaccessible. When the effects of the drug had worn off he was none the worse for his experience although three months later he relapsed when home on trial.

The subjects treated with methedrine showed no disorders of perception either of their own body or of the external world.

Comparison of the Two Drugs.—A property common to both drugs is their capacity of intensifying the symptomatology and accentuating the clinical picture. In doubtful cases this has proved to be a real help in the diagnosis. Both drugs tend to increase tension as indicated by the appearance of cataleptic phenomena, by abreaction, and by the uncovering of delusional material. In this respect, and in the doses used, methedrine seemed to be more effective than L.S.D. Methedrine also induced hallucinations in schizophrenic patients more readily than L.S.D. Insomnia frequently followed the injection of methedrine, but not of L.S.D.

The chief point of difference between the two drugs is in their influence on the affect. The appearance of rapid mood swings, with predominant euphoria, seemed to be a feature of L.S.D. action only.

Biochemical Observations

Plasma Adrenaline Levels.—The changes in the plasma adrenaline concentration observed after the administration of the two drugs are recorded in Figs. 1–4. The results have been expressed as percentage differences from the pre-injection values. The thin lines represent the individual observations, while the heavy lines show the means of the individual observations after a given time interval, together with their standard errors.

The initial concentration of plasma adrenaline, determined as the mean of 23 observations, was $3{\cdot}57 \pm 0{\cdot}084$ μg./l. with a range from 2·80 to 4·26 μg./l. These figures are very close to those previously found (Weil-Malherbe and Bone, 1952).

Though there were considerable individual

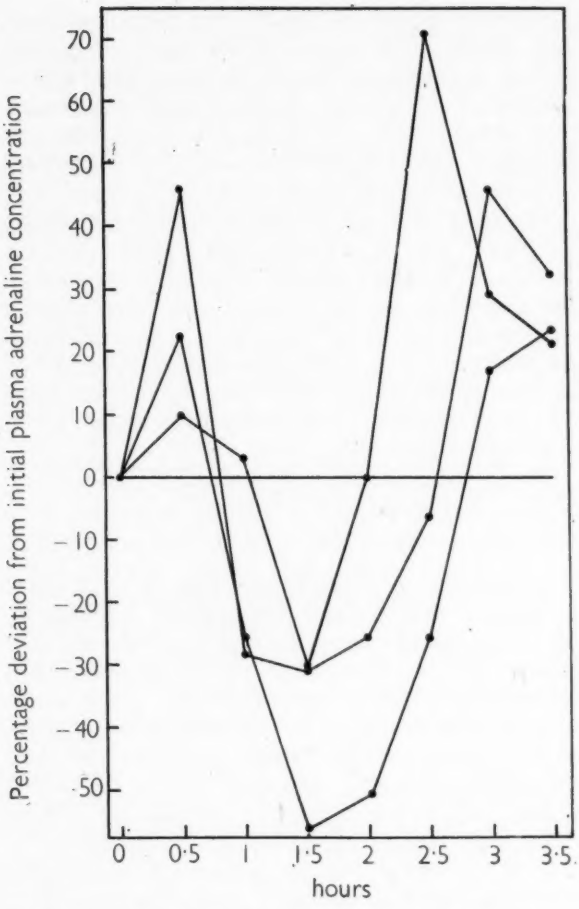

FIG. 1.—The effect of 40 to 60 μg. L.S.D. (by mouth) on the plasma adrenaline concentration.

variations in the response of the plasma adrenaline level to the administration of the drugs, the trend was similar in all cases and with both drugs. Broadly speaking, three phases could be distinguished: (1) an initial rise of plasma adrenaline; (2) a drop well below the base line; and (3) a second rise to the level of the base line or above it.

The greatest variations between individual cases concerned the extent and duration of the first phase, especially when methedrine had been injected. While in some cases the initial rise of adrenaline was pronounced and lasted for 10 to 20 minutes, it was less marked and of short duration in others. In four of the cases injected with methedrine phase 1 was completely absent and the plasma adrenaline level showed a drop without any significant rise preceding it. These cases were considered separately and designated as "Type 2" (Fig. 4). Clinically three of them were diagnosed as schizophrenia and one as psychopathic state. Of the seven cases which showed a "Type 1" response, i.e. a well-marked phase 1 (Fig. 3), four were schizophrenics and three were psychopaths or neurotics. There was thus no obvious correlation between reaction type and diagnosis either in these experiments or in those performed with L.S.D., and in view of the small number of cases the results were not classified according to diagnosis.

Similar differences were observed after the intravenous injection of L.S.D. (Fig. 2). Though an initial rise of the plasma adrenaline level was found in four cases, it had always subsided after 10 minutes; in the other cases this phase was not in evidence at all. The course of events seemed to be similar to that after methedrine injection, but it seemed to proceed faster. Thus, the lowest level of plasma adrenaline was usually observed after five to 10 minutes in the L.S.D. experiments and after 20 to 30 minutes in the methedrine experiments. It is interesting to note that in the curves of plasma adrenaline concentration which were recorded after the *oral* administration of L.S.D. the three phases are well defined (Fig. 1). Though drawn on a different time scale, these curves more closely resemble some of the methedrine curves presented in Fig. 3 than do those obtained after the intravenous injection of L.S.D. and it seems reasonable to attribute the difference to the different rate of entry into the circulation.

In consequence of the different speed with which the three phases develop in different cases there is a considerable overlap when the individual curves are superimposed and many values which are

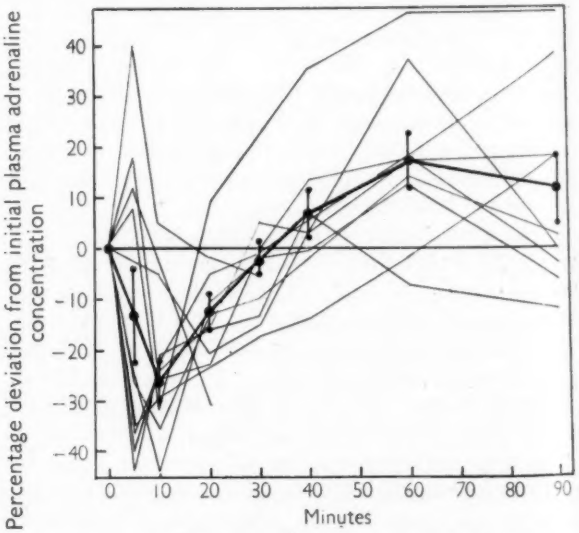

FIG. 2.—The effect of an intravenous injection of L.S.D. (40-60 μg.) on the plasma adrenaline concentration.

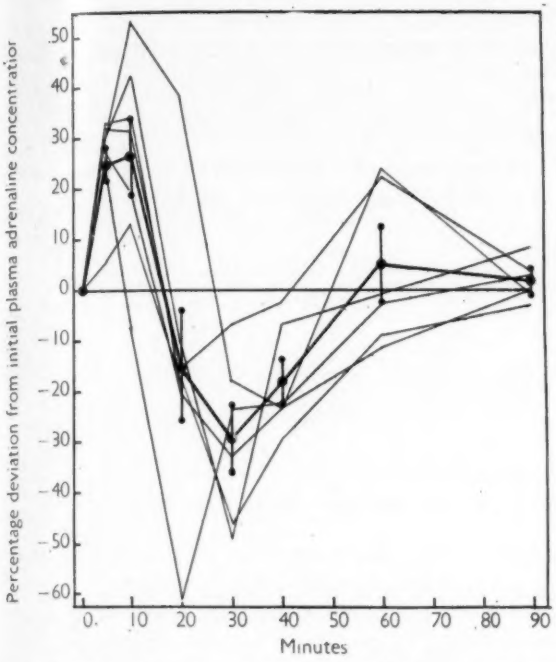

FIG. 3.—The effect of an intravenous injection of methedrine (40–60 mg.) on the plasma adrenaline concentration : Type 1.

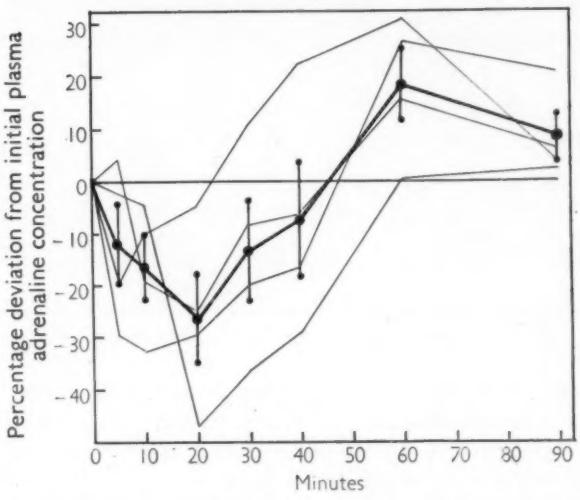

FIG. 4.—The effect of an intravenous injection of methedrine (40–60 mg.) on the plasma adrenaline concentration : Type 2.

significant in themselves tend to cancel each other out in the aggregate. The statistical significance of the means is thereby reduced. In spite of this, the main effects are statistically significant (Table II).

Blood Sugar Levels.—The percentage changes in blood sugar concentration after the injection of methedrine or L.S.D. are shown in Table III.

A significant rise of the blood sugar, by about 20%, occurred after 30 to 40 minutes in those patients who reacted to methedrine injection with an initial rise of the adrenaline level (Type 1). By contrast no such blood sugar rise was found in those cases in which the initial adrenaline rise was absent (Type 2) and a slight blood sugar rise of doubtful statistical significance was only found after 90 minutes. After the intravenous injection of L.S.D. a slight blood sugar rise, amounting in the average to about 6%, occurred ; it is on the borderline of statistical significance.

No clear-cut results were obtained after the

TABLE II

MEAN VALUES OF PERCENTAGE CHANGES OF PLASMA ADRENALINE CONCENTRATION AFTER INTRAVENOUS INJECTION OF L.S.D. OR METHEDRINE AND THEIR STATISTICAL SIGNIFICANCE

	Minutes after Injection						
	5	10	20	30	40	60	90
				L.S.D.			
Mean % change ..	−13·2	−26·2	−12·7	−2·5	+6·9	+17·2	+11·4
S.E.	9·29	3·93	3·62	3·76	4·88	5·54	6·81
N†	10·0	9·0	10·0	10·0	9·0	9·0	9·0
t*	—	6·66	3·51	—	—	3·10	—
P*	—	<0·01	<0·01	—	—	0·015	—
				Methedrine Type 1			
Mean % change ..	+24·6	+26·3	−15·2	−29·5	−18·1	+4·9	+1·6
S.E.	3·54	7·66	10·88	6·71	4·27	7·44	2·63
N	7·0	7·0	7·0	7·0	7·0	6·0	6·0
t	6·85	3·43	—	4·40	4·24	—	—
P	<0·01	0·015	—	<0·01	<0·01	—	—
				Methedrine Type 2			
Mean % change ..	−12·0	−16·5	−26·5	−13·5	−7·6	+18·2	+10·2
S.E.	7·70	6·18	8·65	9·82	11·08	6·86	4·62
N	4·0	4·0	4·0	4·0	4·0	4·0	4·0
t	—	—	3·06	—	—	—	—
P	—	—	0·06	—	—	—	—

* Values of t (mean/S.E.) and P (probability of chance variation) are presented only where the mean changes are significant or nearly significant.

† N = no. of observations.

TABLE III

MEAN VALUES OF PERCENTAGE BLOOD SUGAR CHANGES AFTER INTRAVENOUS INJECTION OF L.S.D. OR METHEDRINE

	Minutes after Injection						
	5	10	20	30	40	60	90
				L.S.D.			
Mean % change ..	+1·04	+3·81	+1·65	+5·67	+5·78	+1·94	+8·18
S.E.	1·61	2·13	1·78	1·71	2·07	1·97	3·36
t*	—	—	—	3·32	2·80	—	2·43
P*	—	—	—	0·01	0·028	—	0·04
				Methedrine Type 1			
Mean % change ..	+6·11	+7·21	+14·67	+20·56	+20·83	+22·52	+15·80
S.E.	2·56	4·27	4·57	3·42	5·17	7·77	4·27
t	2·39	—	3·20	6·0T	4·03	2·90	3·70
P	0·06	—	0·02	<0·01	0·01	0·06	0·02
				Methedrine Type 2			
Mean % change ..	+0·5	+5·6	+4·3	+3·4	+4·2	+5·5	+11·8
S.E.	3·55	6·19	4·27	4·93	3·84	3·73	3·57
t	—	—	—	—	—	—	3·31
P	—	—	—	—	—	—	0·05

* Values of t and P are presented only where the mean changes are significant or nearly significant. No. of observations as in Table II.

oral administration of L.S.D. A slight initial increase of the blood sugar concentration was probably induced by the lactose powder as a diluent for the crystalline L.S.D.

Correlation of Clinical and Biochemical Events

On the whole, the phase of falling adrenaline concentration seemed to be associated with relaxation and euphoria, that of rising adrenaline concentration with tension and anxiety, often accompanied by a sensation of shivering and an appearance of goose-flesh. The case of a middle-aged woman suffering from endogenous depression has been described in an earlier section, who, 60 minutes after an injection of L.S.D., became extremely agitated and screamed continuously for about two hours. This case was also remarkable in showing an elevation of the plasma adrenaline concentration by about 50% above the starting value in the 60- and 90-minute samples, i.e. during the state of excitement (Fig. 2).

Until more is known about the response of the blood adrenaline level to the action of pharmaca and its bearing on psychological phenomena the significance of our findings cannot be fully assessed. One point, however, has clearly emerged: there is a great similarity between methedrine and L.S.D. not only in clinical effects, but also in their effects on the blood adrenaline level, a fact which strongly suggests that both effects are correlated.

SUMMARY

d-N-Methylamphetamine hydrochloride ("methedrine") in doses of 40 to 60 mg. and lysergic acid diethylamide (L.S.D.) in doses of 40 to 60 μg. were given by intravenous injection to patients suffering from various mental disorders and their clinical and biochemical effects studied.

After an initial phase of relaxation both drugs produced an aggravation of the clinical picture: while depressive patients became more retarded and depressed, or more agitated, schizophrenic patients showed signs of increased withdrawal and tension and an accentuation of catatonic and cataleptic features. Abreaction frequently occurred, especially in psychoneurotic patients.

Rapid mood swings were sometimes observed after the injection of L.S.D. Methedrine did not produce this effect, but it more readily provoked hallucinations in schizophrenic patients.

The biochemical studies consisted in the determination of the plasma adrenaline and blood sugar concentrations. The effects of both drugs on the plasma adrenaline level were similar. Three phases could be distinguished after the injections: an initial rise of the adrenaline level, a drop below the starting level, and finally a secondary rise. Individual cases mainly differed in the speed with which these phases followed each other. Sometimes, and especially after the injection of L.S.D., the adrenaline level decreased before the initial rise could be observed. When, however, L.S.D. was given by mouth, the initial increase of the adrenaline concentration was clearly evident.

A moderate increase of the blood sugar concentration sometimes followed the injection of methedrine, but the effects of L.S.D. on the blood sugar concentration were hardly significant.

We wish to thank Messrs. Sandoz Ltd. for a generous gift of lysergic acid diethylamide. We gratefully acknowledge the technical assistance of A. D. Bone.

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INVESTIGATION OF AMNESIC DEFECTS BY PROGRESSIVE PROMPTING

BY

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There appears to be a growing tendency in the recent literature to ascribe the defects of memory seen in organic amnesic states to difficulties of activation (recall) rather than to those of registration or organization of impressions. This was foreshadowed by the clinical observations of such workers as Korsakoff (1889) and Bonhoeffer (1904), who remarked that amnesic patients might be able to find their way around the wards in which they lived, although they would deny, as soon as removed from these surroundings, that they had ever been inside a hospital ward. Although Gillespie (1937) argues from such observations that "the continuity of personal identity and mechanical memory are separate phenomena", the evidence can also be interpreted in terms of inertia or inaccessibility of those memories which are not reinforced by perceptual stimuli.

Such an interpretation is supported by the observations of Grünthal (1923) who found that much past material for which a patient is ostensibly amnesic may be recovered if questions are put to him in such a way as partially to reinstate the forgotten situations. Experiments on learning conducted by Brodmann (1904) and Gregor (1909) with amnesic patients also demonstrated that the apparently forgotten leaves traces which may be seen in a saving on the number of repetitions required for re-learning. Schilder (1942) concludes from a consideration of this evidence that "a psychic experience once conceived does not completely disappear from the psychic field" but "becomes paler in the course of time. . . It can be evoked when the immediate situation demands it".

More recent experimental confirmation of this hypothesis has been forthcoming from studies of amnesia following electric convulsion treatment (E.C.T.). Mayer-Gross (1943) and Zubin (1948) both report that recognition is significantly less severely affected by this treatment than recall, and Janis (1950) further found that past experiences which patients cannot recall when first asked about them may be recovered if the patients are allowed the opportunity to "work on" their memory.

Recent animal experiments carried out by Klüver and quoted by Lashley (1950) point in the same direction and have led the latter to define amnesia as "a lowered level of vigilance, a greater difficulty in activating the organized patterns of traces".

One difficulty in assessing the clinical evidence in this field is the lack of systematic comparison between the availability of memory in normal and abnormal subjects. A study of the availability of memory in general, in relation to the total amount of material remembered, is necessary before organic amnesia can be considered solely in terms of inertia of mental functions. An experimental technique has been designed in a preliminary attempt to meet this need, and the result of its application in a small group of subjects is described in the present paper.

Method and Procedure

The experiment was conducted on patients between the ages of 17 and 60 in the United Oxford Hospitals. The term "amnesic state" refers to patients who appeared sufficiently alert and rational to carry on coherent conversations, but who claimed to have little recollection of their experiences after comparatively short intervals. Intensive testing usually revealed the presence at this time of serious defects in intellectual ability, but the memorizing defect remained relatively the most outspoken disturbance. The majority of patients presenting this condition were suffering from concussional head injuries, intracranial tumours, or tuberculous meningitis.

The test material consisted of (1) a sheet of paper on which were painted silhouettes of the following six animals: dog, rabbit, goose, elephant, cat, horse; (2) six booklets each consisting of a series of nine inkblot sketches graded from a shapeless blot in progressive approximations to a picture identical with one of the animals on the first sheet (Fig. 1). The subjects were presented with the sheet of pictures and asked to name and remember the animals on it. Two hours later they were asked to name as many of the animals as they could recall. For each animal that they failed to name they were then shown the first

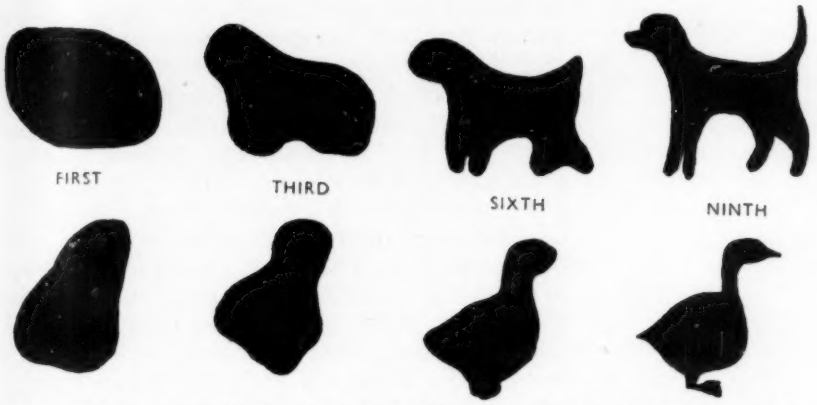

FIG. 1.—Samples of material, showing the first, third, sixth, and ninth pictures in two of the booklets. The ninth picture is identical with the one seen previously.

sketch of the appropriate booklet, with the following instructions :—

" Let me give you some help. As I turn over these pages, each picture will become more and more like one of the animals you have forgotten. Tell me as soon as you see what animal these pictures are going to turn into, or as soon as you remember any of the animals you haven't yet mentioned."

The patient's responses to each picture were recorded. Every time a patient ventured an opinion as to the final outcome of the series, he was asked, " Do you remember seeing that on the sheet of paper before " ? If he mentioned an animal already named, he was told, " But you remembered that already. This is going to be one you haven't told me about." Other incorrect suggestions were left uncorrected.

The number of pictures in a series which had to be shown to a subject before he remembered having seen the original was taken as the number of prompts given to him. It may be mentioned that none of the subjects taking part in this experiment when recalling having seen a certain animal failed to identify their memory with the original picture (re-duplicative paramnesia, Pick, 1903). Had they done so, it would have been necessary to treat the results in some different way.

The test was given to 31 patients from the medical and surgical wards presenting organic amnesic states, and to 20 patients from the same wards with no history or sign of memory disturbance, the control group. The control group was divided into two halves, as closely matched as possible for disability, age, and length of stay in hospital. One half was again tested for their recall after four days, and the other half after seven days. Unfortunately, only six of the amnesic patients were in the same mental state and available for retesting seven days after the original exposure.

The responses were scored according to the following points : (1) number of pictures recalled without prompting ; (2) number of pictures recalled or recognized with the aid of prompting where necessary.

On those pictures not recalled alone, but recalled with the aid of some promptings, the following additional facts were noted : (3) number of promptings needed to secure correct " guess " of what animal the pictures would turn into ; (4) number of promptings needed to secure recollection of its previous exposure.

Results

The distribution of the control and amnesic subjects according to the number of pictures (1)

TABLE I

DISTRIBUTION OF SUBJECTS ACCORDING TO NUMBER OF PICTURES RECALLED WITHOUT AND WITH PROMPTING WHERE NECESSARY

No. of Pictures Recalled per Subject	Control						Amnesic			
	Recalled without Prompting			Recalled with Prompting where Necessary			Without Prompting		With Prompting where Necessary	
	2 hours	4 days	7 days	2 hours	4 days	7 days	2 hours	7 days	2 hours	7 days
6	7	2	2	19	9	5	—	—	19	1
5	7	6	2	1	1	4	5	—	8	1
4	5	1	1	—	—	1	9	2	4	2
3	—	1	5	—	—	—	10	1	—	1
2	1	—	—	—	—	—	5	—	—	—
1	—	—	—	—	—	—	1	1	—	1
0	—	—	—	—	—	—	1	2	—	—
Average	4·95	4·9	4·1	5·95	5·9	5·4	3·3	1·3	5·5	3·8
Proportion of pictures recalled	0·825	0·816	0·683	0·99	0·98	0·9	0·55	0·21	0·92	0·63

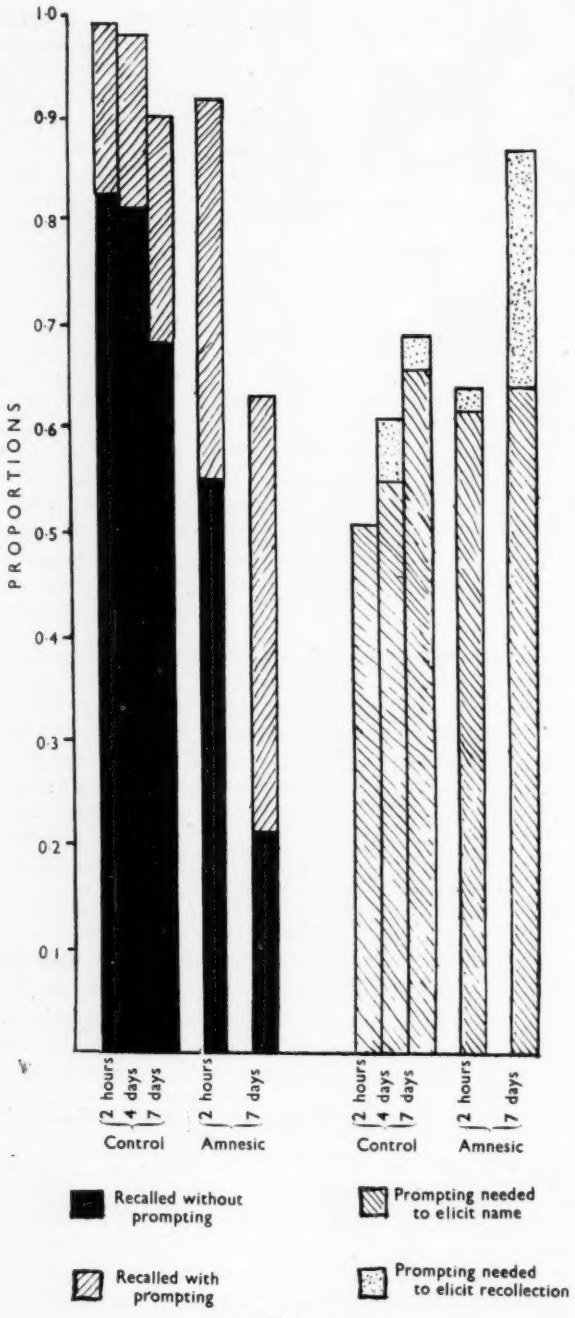

FIG. 2

recalled without prompting, and (2) the number recalled with the aid of prompting where necessary is shown in Table I and in Fig. 2, columns 1–5. It will be seen that after equal time intervals the amnesic subjects recall and recognize many fewer pictures than the control group. Both groups show a decline in the number of pictures recalled and recognized after an increased time interval, but the decline is quicker and greater in the amnesic group than in the control group. The ratio of the material recalled without prompting to the material recalled with prompting is greater in the amnesic group after both time intervals, and increases in both groups with the lapse of time.

For the pictures not recalled alone, but recalled or recognized with the aid of prompting, the distribution of the subjects according to the average number of promptings needed per person to secure the naming of the pictures and those needed to secure recollection are shown in Tables II and III and in Fig. 2 columns 6–10. It will be seen that the amnesic group does not require many more promptings in order to name the pictures than the control group, but it does require considerably more promptings in order to recollect having seen the pictures before. For both naming and recollection of the pictures an increasing number of promptings is needed with the lapse of time in both groups of subjects.

There was some variation between the number of promptings needed for the naming and recollection of the different pictures, but the difference between the amnesic and control groups was consistent for all pictures.

Interpretation and Conclusions

Organic memory defects have been ascribed by many recent writers to the inaccessibility of memories rather than to their absence. The experiments reported here suggest, however, that the availability of particular memories is relative to the total amount of material remembered, and may be retarded in certain conditions in both amnesic and normal subjects. Thus, although the gain obtained through prompting is relatively greater after a given time interval in the amnesic than in the control subjects, there is also among the former relatively more material for which the subjects remain totally amnesic. This suggests that amnesia cannot be wholly accounted for by inaccessibility as measured by recognition, although recognition and recall appear to represent different degrees of availability. It is not denied, however, that further evidence of the after-effect of a previous experience might be gained through different techniques, such as barbiturate hypnosis (Russell and Nathan, 1946), or the measurement of behaviour changes (Williams, 1950).

There remains the question, To what is the lack of availability due? Is it due in the situation described here to the difficulty found in responding to promptings, a defect of perception rather than of memory?

TABLE II

DISTRIBUTION OF SUBJECTS ACCORDING TO AVERAGE NUMBER OF PROMPTINGS PER PICTURE NECESSARY TO ELICIT NAMING OF ANIMAL FOR ANIMALS NOT ALREADY RECALLED

Average No. Promptings per Picture to Elicit Name	Control			Amnesic	
	2 hours	4 days	7 days	2 hours	7 days
8·6–9·0	—	—	—	—	—
8·1–8·5	—	—	—	—	—
7·6–8·0	1	—	—	—	—
7·1–7·5	—	—	—	2	—
6·6–7·0	—	1	2	6	1
6·1–6·5	—	—	2	2	1
5·6–6·0	1	1	2	5	1
5·1–5·5	—	—	1	4	—
4·6–5·0	4	2	1	3	2
4·1–4·5	—	—	—	6	1
3·6–4·0	5	3	1	—	—
3·1–3·5	—	—	—	—	—
2·6–3·0	—	—	—	—	—
2·1–2·5	—	—	—	1	—
1·6–2·0	—	—	—	—	—
1·0–1·5	1	—	—	1	—
Average per group ..	4·6	5·0	6·0	5·58	5·8
Proportion of prompts needed per picture ..	0·51	0·55	0·66	0·62	0·64

TABLE III

DISTRIBUTION OF SUBJECTS ACCORDING TO AVERAGE NUMBER OF PROMPTINGS PER PICTURE NECESSARY TO ELICIT RECOLLECTION AMONG PICTURES NOT ALREADY RECALLED

Average No. Promptings per Picture to Elicit Recall	Control			Amnesic	
	2 hours	4 days	7 days	2 hours	7 days
8·6–9·0	—	—	—	1	2
8·1–8·5	—	—	—	—	1
7·6–8·0	1	—	1	1	1
7·1–7·5	—	—	—	3	—
6·6–7·0	—	1	1	8	1
6·1–6·5	—	1	2	3	—
5·6–6·0	1	2	2	2	—
5·1–5·5	—	—	—	4	—
4·6–5·0	4	1	1	2	1
4·1–4·5	—	—	—	1	—
3·6–4·0	5	2	—	3	—
3·1–3·5	—	—	—	—	—
2·6–3·0	—	—	—	—	—
2·1–2·5	—	—	—	1	—
1·6–2·0	—	—	—	—	—
1·0–1·5	—	—	—	1	—
Average per group ..	4·6	5·5	6·2	5·8	8·0
Proportion of prompts needed per picture ..	0·51	0·61	0·69	0·64	0·87

Is it due to the difference of " mental set " present at the re-test, or is it due to fading of memories with the lapse of time ?

The findings cannot be explained entirely in terms of perceptual defects, because, as seen from Table II, the amnesic groups were able to name the pictures nearly as well as the control subjects. Nor can the results be interpreted in terms of " set to remember " or to the presence of discharged and undischarged tension systems (Zeigarnik, 1927), for, although at the delayed test the subjects had already been once asked for their recall and might thereafter have put the matter out of their minds, this condition applies to the 10 control subjects retested after four days as well as to those retested after seven days, between which groups significant differences were still found. The passage of time, however, seems to be accompanied by a decreased availability of memories in the control group which is seen in two aspects : in the decreasing ratio of material recalled without prompting to that recalled with, and in the number of promptings needed per picture to secure recall. In the amnesic subjects the lapse of time is accompanied by similar changes, but the speed of change is quicker than it is in the control group. In some respects (see Tables II and III) the memories of an amnesic subject after two hours are in the same state of availability as are those of a normal person after four to seven days.

These results suggest that the chief difference between the memories of normal and amnesic subjects does not lie in the availability of memories *per se*, but in the susceptibility of memories to the effects of time. I have reached a similar conclusion from a different type of experiment on different subjects (Williams, 1952). Although this has probably been recognized by the majority of clinicians (Schilder, 1942) it is considered worth emphasizing again as it does not appear to have received previous experimental verification, and the duration of memory traces does not up till now feature as a dimension measured by any of the standardized memory tests.

Summary

A technique has been devised to study the accessibility of memories in relation to the total amount of material remembered.

When material cannot be recalled progressive promptings are applied until the original situation is reconstructed.

An experiment using this technique with 20 control and 31 amnesic subjects at different time intervals demonstrates that the memory of amnesic subjects is less accessible (relative to the amount spontaneously recalled) than is the case in normal individuals, but that inaccessibility alone cannot account for all the material forgotten by amnesic patients.

Accessibility decreases with the lapse of time, but does so more quickly in amnesic than in normal subjects. After two hours the amnesic subjects show much the same condition as the control group after four to seven days.

It is concluded that inaccessibility of memories is not in itself the prime difference between amnesic and normal subjects, but that a more important difference is the speed with which this accessibility diminishes.

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THE PARAESTHESIAE INDUCED BY COLD

BY

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The paraesthesiae which occur during and after the occlusion of the circulation to a limb have been extensively studied by Bazett and McGlone (1932), Lewis, Pickering, and Rothschild (1931), Zotterman (1933), Kugelberg (1944), Weddell and Sinclair (1947) and Merrington and Nathan (1949). Paraesthesiae induced by subjecting a limb to cold have, however, received but scant attention. Wolf and Hardy (1941) in their studies on pain in a limb induced by cooling observed the occurrence of " pins and needles " when the hand was placed in water below 12° C., and wrote of the subject being " forced to withdraw his hand owing to the suffering imposed by the growing intensity of the pins and needles sensation ". In similar studies Kellgren, McGowan, and Hughes (1948) noted, besides cold pain, two further sensations which they called skin pain and tingling. Bickford (1939), when cooling peripheral nerves rapidly, observed pain but did not mention other sensations. Sinclair and Hinshaw (1951a) specifically denied the occurrence of any tingling or " touch paraesthesiae " during the development of cold blocks of the ulnar and lateral popliteal nerves. These different accounts may be due in part to the fact that each study was concerned with a particular feature rather than with the whole experience when a limb or a nerve was subject to cooling.

The present study is concerned with establishing what spontaneous, sensory experiences occur when a limb is cooled. It further seeks to locate the site of origin of these subjective phenomena, and the nervous pathways which conduct them to the sensorium. It also endeavours to find the relationship of these phenomena to those produced by ischaemia of a limb. All authors have agreed that pain can be induced by cooling a nerve, and as the features of this cold pain have been extensively studied by Wolf and Hardy, attention here will be mainly devoted to the other phenomena observed.

Experiments

The observations reported here were made on six healthy subjects. The findings were substantially the same in each one ; the relevant differences will be mentioned in the discussion.

When the hand up to the level of the wrist is placed in water at 4° C. the first sensation experienced is that of intense cold. After 10 to 15 seconds a dull, diffuse, aching pain is felt in the hand and often in the forearm above the water level, especially along the ulnar border. This aching pain rapidly increases to its maximum severity, and then slowly subsides, ceasing in five to seven minutes. Between one and two minutes after immersion, while the pain is still present, there begins in the hand a very mild, diffuse, tingling sensation felt best in the palmar aspect of the fingers. In quality it is most like ischaemic tingling, but lacks the discrete, irregular feeling of post-ischaemic pricking. It is not affected by moving the fingers, but light pressure on the skin temporarily relieves it. This tingling sensation lasts from three to five minutes though the end-point is difficult to gauge. In addition to the dull pain and the tingling sensation already described, there begins about three minutes after immersion a severe burning or smarting sensation felt diffusely in the skin of the hand. This increases in severity until it becomes uncomfortable. Most subjects consider this to be by far the most unpleasant sensation of the three. It seems only to occur in very cold water of 4° C. or less, and may last for five or six minutes (Fig. 1). These three are the phenomena that have been observed, namely, cold pain, a tingling sensation, and a burning sensation. These terms will be used to designate them in this paper.

Threshold for Tingling and Burning.—The hand was placed in water at 37° C. for five minutes and then transferred to water at different temperatures. It appeared that the temperature level at and below which the tingling sensation could be induced was about 15° C. It varied slightly in different subjects from 13° C. to 15° C. but was constant in any one subject. The threshold for the burning sensation was much lower. It was never experienced

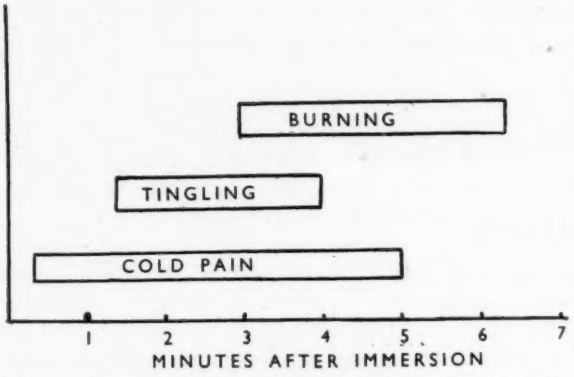

FIG. 1.—Diagram of the onset and duration of paraesthesiae following immersion of the hand in water at 4° C.

unless the temperature of the water was 4° C. or lower.

Effect of Range of Temperature Change.—The possibility that the tingling and burning might be dependent on the range of temperature change rather than on the final level reached was next investigated. Placing the hand on separate occasions in water at 37° C., 22° C., and 16° C. for five minutes and then transferring it to water at 10° C. produced in each instance tingling sensations having the same degree of severity and time of onset. The burning sensation likewise did not appear to be dependent on the range of temperature change. Transferring the hand from water at 37° C. and 19° C. to water at 2° C. produced a burning sensation of like severity and time of onset.

Effect of Rate of Cooling.—Instead of transferring the hand immediately from water at one temperature to water at a lower temperature, the temperature of the water in which the hand was immersed was lowered at the approximate rate of 1° C. per minute from 18° C. to 13° C. Cold pain was not felt, but the tingling sensation appeared at the same temperature level as it had when the temperature was lowered suddenly. Similarly the burning sensation appeared when the temperature reached 4° C. even with slow cooling. Cold pain, therefore, seems to be dependent to a great extent on the rate of temperature change, whereas tingling and burning depend more on the actual temperature reached.

Severity of Tingling and Burning in Relation to Temperature.—Though the temperature thresholds at which the tingling and burning sensations appeared were constant, the lower the temperature the more severe was the tingling or burning. Thus with the right hand in water at 10° C. and the left in water at 1° C. more severe tingling was experienced in the left hand. Over the range of 15° C. to 0° C. used in these experiments the lower the temperature the more severe the tingling and the longer its duration. The short range from 4° C. to 0° C. made observation of a difference in the degree of burning more difficult but it did seem that the sensation was more severe at 0° C. than at 4° C.

Effect of Further Lowering Temperature after Cessation of Tingling.—With the hand in water at 10° C. the tingling sensation appeared as usual. Three minutes after all tingling had ceased the hand was transferred to water at 4° C. Tingling was again experienced, beginning at one minute 45 seconds after immersion, and was still present when it was obscured by the severity of the burning which began at two minutes 50 seconds.

Effect of Removing Hand from Cold for a Period.—After being in water at 37° C. for five minutes the hand was transferred to water at 12° C., whereupon the usual tingling appeared. After five minutes, when all tingling had ceased, the hand was returned to 37° C. for two minutes, and then re-immersed at 12° C. On this occasion neither tingling nor cold pain was felt. The experiment was repeated but this time the hand was left at 37° C. for three minutes. When it was re-immersed in water at 12° C. cold pain developed followed by the tingling sensation. When the hand after preliminary cooling was immersed in water at 16° C. it required five minutes at this temperature before re-immersion in cold water produced tingling again. It seems, therefore, that the changes in the nerve which permit the redevelopment of the paraesthesiae on further cooling proceed more rapidly at a higher temperature.

The period above threshold required for the burning sensation to recur on cooling the hand again was similar. Thus, after being in water at 1° C., a period of at least five minutes at 18° C. was required before re-immersion at 1° C. was followed by a recurrence of the burning.

Site of Origin of Paraesthesiae.—It was found that immersing one finger only on the right and the whole hand on the left in water at 3° C. produced tingling and burning of equal intensity on both sides. In the case of the right hand the sensations were felt only in the immersed finger, while on the left side they were experienced diffusely in the whole hand. Thus, though the intensity of the sensations seemed the same in comparable areas on the two sides, the greater area of burning on the left made the total discomfort greater on that side. When the limb as far as the elbow was immersed in water at 3° C. tingling and burning occurred, but were con-

fined to the hand. Nothing but a cold sensation and cold pain were felt in the forearm.

In the next experiment ice was placed around the groove at the elbow in which lies the ulnar nerve, the forearm and hand being in a room temperature of 21° C. The tingling sensation developed, but was felt only in the little and ring fingers and the ulnar border of the hand. Cold pain also appeared, but was felt around the immersed elbow and down the ulnar border of the forearm. No cold pain was felt in the hand. The burning sensation was not felt at all, neither in the elbow, hand, nor fingers.

A further step was to place the hand in 8% celloidin in equal parts of ether and alcohol (Merrington and Nathan, 1949). As this dries there develops an intense pallor of the skin, and on removing the celloidin a typical post-ischaemic hyperaemia appears. The assumption was made that this ischaemia would render the sensory end-organs functionless. Ten minutes after a celloidin coat was thus applied the hand was immersed in water at 2° C. whereupon cold pain, tingling, and burning all developed as usual. From these experiments it is concluded that cold pain and tingling arise in the nerve trunks. The burning sensation, however, appears to arise more peripherally.

Relation to Ischaemic Paraesthesiae.—The possibility that the tingling sensation was a mild form of ischaemic paraesthesiae induced by the vasoconstriction caused by the cold was investigated. A sphygmomanometer cuff was placed on the arm above the elbow and inflated to 200 mm. of mercury. Ischaemic paraesthesiae developed as usual, and when they had entirely ceased the hand was placed in water at 5° C. The tingling sensation developed in the same manner as when the circulation was not occluded. This indicates that the tingling sensation due to cold may occur after the paraesthesiae due to the development of ischaemia have ceased.

Sensory Fibres Involved in the Sensations.—A cuff was placed on the arm and inflated to 200 mm. of mercury, the forearm and hand being immersed in water at 37° C. Twenty minutes after occlusion touch sensibility in the hand was lost even to a nylon thread of 70 g. tension. The threshold for pain as aroused by pinprick was at this stage unchanged. The hand was then transferred to water at 3° C. Cold pain and the burning sensation developed, but no tingling was felt. This failure to arouse tingling at this temperature strongly suggests that this form of paraesthesiae is dependent upon the integrity of the fibres which subserve touch sensibility, this being the only form of sensation lost at this stage.

In the next experiment a cuff was placed on the arm and inflated to 200 mm. of mercury but left *in situ* for 45 minutes. At this stage touch sensibility was lost to a nylon thread of 70 g. tension, a thrust with a 140 g. pin produced no pain, a test-tube containing water at 60° C. caused no sensation, but a cube of ice applied to the skin of the fingers produced a burning sensation with no feeling of cold. A test-tube containing water at 4° C., however, was not felt at all in the fingers. Squeezing the webs of the fingers or the finger tips also produced an extremely unpleasant burning feeling indistinguishable from that produced by ice. When the whole of the fingers was immersed in water at 4° C. the burning sensation developed to a severe degree of intensity. From this experiment it seemed that the burning sensation was carried by those fibres which carry pain from structures below the skin. The fact that ice, though producing no sensation of cold, was able to give rise to a burning sensation, however, prevented a definite conclusion from being reached.

In an endeavour to produce a greater and earlier loss of cold sensibility a cold block of the ulnar nerve was next induced. The groove containing the left ulnar nerve at the elbow was immersed in a mixture of ice and water at 1° C., the forearm and hand being in air at 21° C. Anaesthesia was allowed to develop until ice placed on the little finger produced neither cold nor burning sensations. Water at 55° C. was still felt as hot, and a 90 g. pin still produced pain. At this stage the little fingers of both hands were immersed in water at 1° C. The burning sensation developed after about one minute and slowly increased, being of equal intensity on both sides. From this it seemed clear that the burning sensation could be produced in the absence of sensibility to cold.

Pain from structures below the skin is carried by C fibres which have been shown by Gasser and Erlanger (1929) to be the first to be affected in a procaine block. In the next experiment the ulnar nerve at the elbow was infiltrated with 1% procaine. As soon as the block began to develop the little fingers of both hands were immersed in water at 1° C. At this stage the sensory state of the little finger on the side of the block was that touch with a nylon thread of 4 g. tension was unchanged as also were cold and warmth. Pain from the skin required a 36 g. pin compared with a 13 g. pin before, and pain from deep tissues could not be aroused even with 20 lb. pressure from an algesio-

meter. When the little fingers were inserted in the water tingling developed as usual. Cold pain and the burning sensation were, however, not felt at all.

The experiment in which applying a test-tube containing water at 4° C. to a small area produced no sensation whereas immersing the whole hand was followed by the burning sensation, suggested that the amount of tissue stimulated was an important factor. As the burning sensation is most intense when the limb is cooled while ischaemic, a cuff was placed on the arm, inflated to 200 mm. of mercury and left for 45 minutes. The tip of one finger was then immersed in water at 1° C. The smarting sensation did not develop until seven seconds after immersion. The finger was removed, the smarting ceased, and then the whole hand was inserted in the water whereupon the smarting developed immediately. This confirmed that the amount of tissue being stimulated was a factor in the development of the smarting.

One further observation was made on a subject who had had the spino-thalamic tract divided on the right side for pain due to secondary carcinoma. On the left foot a 140 g. pin was not felt as pain, and 20 lb. pressure with an algesiometer was likewise painless. Ice and a test-tube containing water at 55° C. were felt merely as touches. The whole of the left foot was inserted in ice and water at 1° C. but neither cold pain nor burning were felt, the patient continuing to converse quite happily. After five minutes the foot was withdrawn. The right foot was then inserted and immediately cold was felt followed by cold pain and smarting. The patient's face was contorted with anguish and despite the utmost encouragement he withdrew his foot, apologising for not being able to continue the experiment. Since the cordotomy the patient had experienced spontaneous tingling in the left foot, and hence observations on cold tingling were not possible.

Discussion

It is difficult to correlate the sensations noted in these experiments with those previously reported in the literature. There appears to be general agreement as to the nature and characteristics of cold pain, and as this has been extensively studied by Wolf and Hardy (1941), and Kellgren and others, (1948) it has received little mention here. The observations made in this study confirm that this pain, which is a dull, diffuse ache, develops when the hand is immersed in water about 16° C. It is felt in the hand and forearm, beginning a few seconds after immersion, and after rising rapidly to a peak at about 60 seconds slowly dies away over a period of four minutes. The lower the temperature of the water the more severe the pain. The temperature change, however, must be sudden, for if the temperature of the water is slowly lowered no pain is felt.

As regards the other sensations, however, the situation is different. Wolf and Hardy mention only one sensation in addition to cold pain, and this they called pins and needles. It began after immersion in water of about 12° C.; at lower temperatures the sensation was so unpleasant as to make the subject withdraw the hand from the water. In the present study the tingling sensation, though beginning just above 12° C., was only of mild degree; it was certainly never of such an intensity as to make the subject discontinue the experiment. The burning sensation, on the other hand, was, in all subjects except one, extremely severe and unpleasant, and it required considerable perseverance to continue the experiment. Wolf and Hardy also noted that, even after 45 minutes' ischaemia, pins and needles appeared when the hand was placed in cold water. In the present study the tingling sensation was not obtained after touch sensibility from the skin was lost by ischaemia. The burning sensation, however, persisted undiminished. It seems, therefore, most likely that the pins and needles sensation of Wolf and Hardy is what has been called here the burning sensation, as the accounts of these phenomena have most features in common.

Kellgren and his colleagues observed two sensations in addition to deep pain. These they called tingling and skin pain. Their tingling sensation is undoubtedly the tingling sensation of the present study. Their skin pain is almost certainly the burning sensation of this paper. The burning sensation was qualitatively like the burning or smarting described by Lewis and Hess (1933) as occurring with prolonged pain arising from the skin. This likeness may well have led to the application of the term " skin pain ".

The other point which must be borne in mind in comparing the reports of different workers is the fact of considerable individual variation in the experience of spontaneous sensory phenomena. Thus, in their studies on post-ischaemic paraesthesiae Merrington and Nathan found marked variations in the individual susceptibility to pricking and tingling, and in the facility with which cooling the limb enhanced the pricking. Likewise Marshall (1952) in a series of cuff tests on healthy subjects found considerable variation from person to person in the ischaemic and post-ischaemic paraesthesiae. Similar variations may well apply to paraesthesiae

induced by cold. In the present study one subject felt only mild burning. When he put his hand in ice and water at 0° C. he experienced very severe discomfort, but considered that this was due to severe cold pain, and not to the burning which was present to only a mild degree.

From the experiments described it seems that the cold pain arises in the nerve fibres at the site of cooling. Thus cooling the hand caused pain in the hand radiating up the forearm for some distance, while freezing the ulnar nerve at the elbow produced pain in the elbow radiating down the forearm, but not felt in the hand.

The tingling behaved somewhat differently. Cooling so small an area as one finger produced tingling in that finger, whereas cooling the whole limb from the elbow down produced tingling only in the fingers and hand and not in the forearm. The significant experiment, however, was that when the ulnar nerve at the elbow was cooled tingling was still felt in the little and ring fingers and the ulnar border of the hand. This, combined with the celloidin experiment, makes it clear that the tingling arises in the nerve fibres and not in the sensory end-organs. This accords with the findings of those who have worked on ischaemic paraesthesiae, for here also the tingling, though felt in the fingers and hand, arises at the site of compression of the nerve. But though the site of origin is the same in ischaemic and cold paraesthesiae they differ greatly in intensity. Ischaemic tingling attains a fairly strong degree of intensity, whereas the tingling induced by cold is a mild or moderate phenomenon. This is true even at temperatures which are sufficient to induce loss of sensation much more rapidly than does ischaemia. Further, the tingling sensation induced by cold could be induced after ischaemic tingling had ceased. This suggests, therefore, that, though ischaemic and cold tingling arise at the same site, the mechanism by which they are produced is different. Sinclair and Hinshaw (1951b) have suggested from their observations on the order in which the various sensory modalities are lost during nerve blocks that the effect of cold and ischaemia on nerve fibres may be fundamentally different.

As for the pathways by which the tingling sensation is carried the cuff experiment showed that the tingling sensation induced by cold could not be obtained when touch sensibility was lost, pain and temperature appreciation still being present in the skin. When a procaine block was induced and pain was lost, while touch to a nylon thread of 4g. tension was still present, the tingling sensation followed immersion in cold water as usual. This is presumptive evidence that the tingling sensation is carried by the fibres which subserve touch sensibility.

The site of origin of the burning sensation is a more difficult problem. As with tingling, when the whole limb to the elbow was immersed in cold water, the burning which arose was confined to the fingers and hand. When, however, the ulnar nerve was cooled at the elbow no burning was felt anywhere. This suggests that cooling a short length of the nerve trunk alone is inadequate to produce the burning. On the other hand if the assumption that the celloidin coat renders the sensory end-organs in the skin functionless is valid, then that experiment would suggest that the sensory end-organs in the skin are not the site of origin of the burning sensation. Furthermore, combining the results of the experiments using ischaemic and cold blocks, when touch, pin, ice, and water at 60° C. were no longer able to arouse sensations from the skin, burning immediately followed immersion of the hand in cold water. This suggests that skin sensation is not essential for this paraesthesia to be felt.

The question of the amount of the limb inserted in the water is also important for the burning sensation. In the experiment in which after 45 minutes' ischaemia first the finger tip and then the whole hand were inserted in water 1° C. the burning developed more rapidly when the whole hand was inserted. From the results of these experiments it seems probable that the burning sensation arises in the tissues deep to the skin.

The nature of the fibres which carry the burning sensation seems fairly clear. Touch, cold, warmth, and pain aroused by pricking the skin could all be abolished, and yet burning was still felt. In the procaine block of the ulnar nerve, however, as soon as pain from the deep tissues was lost neither cold pain nor burning could be elicited. The sum total of these results suggests that the burning sensation arises from the stimulation of the nerve endings which subserve pain from tissues deep to the skin.

In conclusion, therefore, it appears that the application of cold to a limb is able to produce spontaneous sensory phenomena. These differ from those which occur during and after ischaemia and seem to be independent of them.

Summary

When the limb is immersed in cold water there appear cold pain, a dull, diffuse, aching pain; a tingling sensation, which is a diffuse vibrating feeling; and a burning sensation which is a superficial smarting or burning feeling.

The tingling sensation appears after immersion

in water at temperatures below 15° C., arises in the nerve trunk, and is conveyed by the nerve fibres which subserve touch sensibility.

The burning sensation appears only after immersion in water below 4° C.; it arises in the nerve endings subserving pain from tissues deep to the skin.

The phenomena induced by cold are separate entities from those which occur with ischaemia.

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AFFECTIVE EPILEPSY*

BY

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In the early part of this century several writers (Oppenheim, 1906 ; Bratz, 1907 ; Dana, 1907, and others) reported fits which were neither epileptic nor hysterical but which, they believed, were provoked directly by external stimuli, such as slight excitement or over-exertion causing an emotional change. The term " affective epilepsy " was introduced by Bratz and Falkenburg in 1904 to describe these fits, which often resembled the prodromata and aura of true epilepsy but were accompanied by outbursts of emotion and not by epileptic convulsions. When it was found that such cases often turned out to be of organic origin interest in them gradually declined. Now that the psychological aspects of epilepsy are again receiving much attention from clinicians and investigators, however, it may be worth while to reconsider this syndrome of affective epilepsy and in particular to study a case in which it played a prominent part.

Case History

The patient was first admitted to the Valerius Clinic in 1941 at the age of 23. For two years he had suffered from minor fits, which had become more frequent shortly before his admission. There were no convulsions. During these short fits the eyes rolled, or he had a vacant look, or a transient moving of the lips. Consciousness was lowered during the fit, and there was aphasia for about two minutes following the attack. There was amnesia for the fits, although he would remain sitting or standing. There were no complaints of headache, vomiting or vertigo, nor of disturbance of micturition. There were no personality changes.

Neurological examination in November, 1941, showed impaired motor function of the right facial nerve and divergent strabismus to the left. Air-encephalography showed that the anterior horns and, even more distinctly, the diencephalon were displaced to the right. The left anterior horn was displaced slightly upwards, and was slightly flattened. The posterior horns were normal.

Clinical data and ventriculograms indicated that the cause of the displacement must lie basally on the left, rather far forward, almost at the level of the foramen of Monro. There was very little functional impairment. A frontal trepanation was made but inspection of the orbital roof and olfactory nerve showed no trace of tumour. Puncture met with a deep resistance, situated not quite frontally. It was therefore not possible to carry out a radical frontal lobectomy, and there was no point in risking functional impairment for the purpose of exploration. Only subtemporal decompression was carried out, with post-operative *x*-ray treatment. The patient was discharged home, at first quite well ; he gradually became more and more emotional, tired easily, and was infantile in affect.

He was admitted again in November, 1946. For the past year his fits had been accompanied by a curious emotional discharge. After slight excitement, such as entering the lecture-room or sitting in the screen-room, there would be a sudden lapse of fixation in his gaze, a vacant look, a transient moving of the lips. This would be followed by a period of slightly lowered consciousness and then by a violent emotional discharge. He would suddenly start to deliver a speech in a pseudo-language, with mimicry and gestures to match. If the content and sound of his words were disregarded, the affective expression was within normal limits and the modulation of his speech was normal. He would utter incomprehensible words, gesticulating violently as if trying to persuade someone ; clench his fists and pound on the table as if furious. A torrent of words would be released, consisting of apparently meaningless syllables. This would last for about three minutes, towards the end of which he would speak in a lower and lower voice, looking to the left. Finally he would say a few syllables in a wheedling tone, smile contentedly, and the fit would then be over. He would immediately recognize his environment and speak sensibly to those around him. During the emotional outburst he showed a stereotyped automatism of behaviour, but appeared to be fully conscious and in full possession of his faculties, though not normally in touch with his environment.

Neurological examination revealed an end-position nystagmus on the right as well as on the left. Arm and leg reflexes were a little brisker on the right than on the left but there were no pathological reflexes. The diencephalon appeared normal, but both on the left and on the right there was a slightly choked disc. Another air-encephalogram revealed an obstruction of the left interventricular foramen.

From January, 1947, he had irradiation treatment,

* Based on a lecture delivered at the Maudsley Hospital, London, in March, 1952.

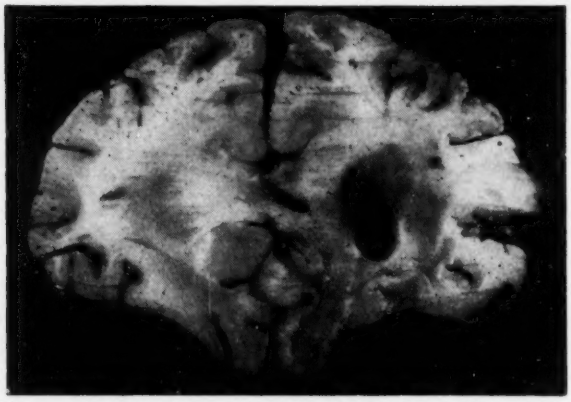

FIG. 1.—The distended anterior horn of the left ventricle is visible. The tumour is localized on the basal side, both right and left.

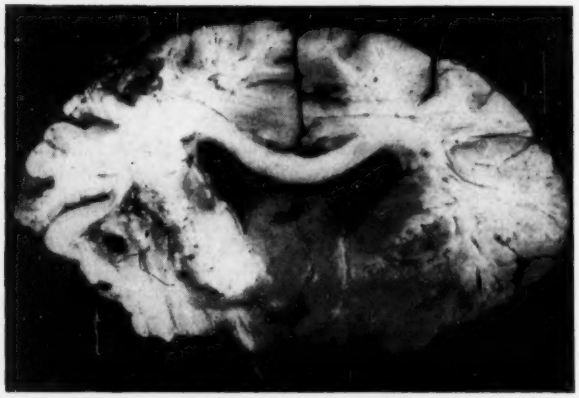

FIG. 2.—This section shows a diffuse mass of tumour in the median region, with a cyst in its centre.

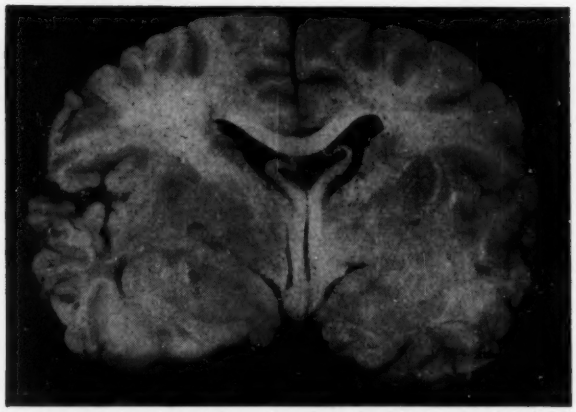

FIG. 3.—The section shows the markedly thickened columns of fornices and bodies of fornices as far as the mammillary bodies.

with some initial success, and he was discharged in February, 1947.

On his third admission, in July, 1949, he presented a puerile euphoria and signs of slight deterioration. An E.E.G. showed slow waves, frontal and temporal, on both sides The most striking feature of his clinical behaviour was that he still showed occasional very violent emotional outbursts. The neurological picture was unchanged.

The patient died in October, 1949, with signs of increased intracranial pressure. There was a gradual lowering of consciousness and he was subcomatose for some days before he died. The diagnosis was the same as eight years earlier: fronto-temporal tumour confirmed by neurosurgical operation.

The post-mortem examination showed that the convolutions of both hemispheres were markedly flattened. Adhesions with the dura were found in the left temporo-parietal region at the site of the old exploratory operation. The extent and type of the tumour are shown by Figs. 1 to 8.

To sum up the histopathological findings, the process extended throughout the basal subcallosal regions of the frontal lobes, the septum pellucidum, the fornices and the hippocampus, extending to the hypothalamus, the thalamus, the lenticular nuclei, and the cortex of the insula. The cingulate gyrus showed diffuse gliosis not clearly continuous with the main tumour mass. The outstanding feature was that the proliferation was practically confined to the rhinencephalon whereas the neopallium had suffered little.

Discussion

The initial problem arises from the emotional outburst. Emotion is a dynamically interrelated whole, at once physiological, psychological, and social. It is in a normal person a highly integrated, self-regulating structure, connected with continuous conscious experience. It is not possible to study the phenomena of emotion without regard to the well known cerebral systems upon which they depend. This patient's clinical behaviour could be attributed to a complex of reverberating circuits, occasionally exhibiting very violent emotional discharges in which he availed himself of the various possibilities of expression in speech, face, and gesture. In this we have to distinguish between the expression of emotion and the experience of emotion.

In 1937 Papez pointed out in his fundamental study, " A Proposed Mechanism of Emotion ", that the hippocampal formation with fornix, hypothalamus, anterior thalamic nuclei, and cingulate gyrus, together with their connexions, constituted a self-regulating system, accurately dealing with feeling tone as well as participating in emotional expression. However, though the patient was under my supervision from 1941 till 1949, the application of this hypothesis to his disorder did not occur to me. I concluded on his first admission that the cause of the displacement evident in the ventriculogram must be a tumour seated basally on the left,

FIG. 4.—The whole hippocampus and the cortex of the hippocampal gyrus are affected. The lenticular nucleus situated above them is completely filled up by neoplastic proliferation; the cortex of the insula, the thalamus, the hypothalamus, and the fornix also show proliferation. The cingulate gyrus is clearly affected, whereas the corpus callosum is not.

FIG. 5.—The hippocampus on the right side in the same cut surface has a slightly swollen appearance. The thalamus is possibly slightly enlarged.

and my diagnosis remained the same when he died eight years later.

There are many indications that the rhinencephalon is largely concerned with emotional functions. This phylogenetically old part of the brain appears to be so strategically situated as to be able to correlate every form of internal and external perception. And, in contrast to the neopallium, the rhinencephalon has many connexions with the hypothalamus; though our intellectual functions are carried on in the newest and most highly developed part of the brain, our affective behaviour continues to be dominated by a relatively crude and primitive system.

The medial wall of the cerebrum is physiologically integrated with the hypothalamus and the lateral wall with the dorsal thalamus. Moreover, obsessive oral utterances can arise from irritation of the cingulate gyrus. In the clinical picture presented by our patient, we are justified, therefore, in suspecting irritation and radiation as consequences of morbid processes in the hippocampus and cingulate gyrus. The question of what our patient was feeling is irrelevant: as Bard (1934) showed, only the cortex is essential to the subjective experience of emotion.

FIG. 6.—Nissl staining reveals that the right hippocampal region contains an excessive proliferation of cells as well as the thalamus and the hypothalamus, while there is unmistakable evidence of this process also in the fornix.

FIG. 7.—Glioblastoma multiforme. There are occasional masses of vascular proliferations, sometimes showing a similarity to glomeruli—" Scherer coils ".

Lesions in the hippocampal formation or, to put it otherwise, in the Papez circuit, may intensively affect the expression of emotional life (anxiety, apprehensiveness, rage, and terror). The question arises whether patterns of emotional discharge may lead to excessive expression if they are not controlled by the neocortex, and whether release of these discharges will be repeated whenever stimulation occurs in the rhinencephalon. Here autochthonous stimuli might have arisen from the pathological glia.

In this case there are arguments for the condition being a developmental disease, and for its being a new growth. It is difficult to determine the original site of the process. Some displacement existed in the anterior part of the left basal region, at the approximate level of the foramen of Monro. The puncture needle met resistance immediately posterior to the frontal region.

Similar tumours have been described. Ostertag (1951) classifies them under a separate heading, gliomata of the allocortex. They are presumed to develop on the basis of developmental disorders. This theory is substantiated by the simultaneous existence of persistent embryonic fissures in the surface of the thalamus and ependymal changes, associated with cortical changes in the form of myelinization gliosis, proliferation of satellite cells, and persistence of the embryonic granular layer. The olfactory parts of the brain are always predominantly affected.

In our case the gliosis in the cingulate gyrus is suggestive of a developmental disorder. The adhesion of the frontal hemispheres on the basal side of the longitudinal fissure is also reminiscent of a malformation. But the intensive proliferation of glia conveys a strong impression of an independent blastomatous process. There is little to support the diagnosis of a diffuse periaxial encephalitis. The naked-eye picture of the hippocampus, which is twice its normal size, indicates a new growth, which is corroborated by the microscopical findings.

So I would prefer to ascribe these diffuse neoplasms to a faulty " ability " of the glial tissue, reminiscent of a systemic disease, such as reticulosis. This view corresponds to the one held by Schwartz and Klauer (1927) who, after reporting their case, concluded :

> " There actually exist blastomatous proliferations of the glial apparatus, arising all at once throughout the system—or in its major parts—from the innumerable autochthonous elements."

In spite of the marked increase of pathological glia, the structure of the cerebral system remained intact in many places. Axis cylinders have rarely been impinged upon, myelin sheaths more, though to a lesser extent than in diffuse sclerosis. We are faced, then, with a systemic disease in the rhinencephalon. But on the other hand the proliferation of glia is, for instance in the left lenticular nucleus, very intensive and without any respect for the preexistent structure ; there were patches of necrosis

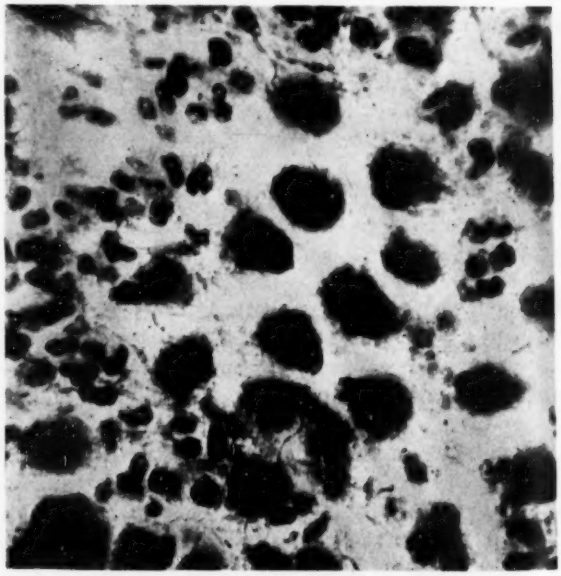

FIG. 8.—Nissl's " *astrocytome à grandes cellules* ".

and vascular proliferations. It might then be inferred that this process started as a fairly benign, slowly growing spongioblastoma and macrocellular astrocytoma, which finally developed into a glioblastoma.

Summary

Summarizing, we have a remarkable process extending through the entire rhinencephalon in a 31-year-old man, who had had fits for 10 years and, during the last four years, symptoms of affective epilepsy. The three-fold interest of the case lies in the clinical value of the syndrome as a guide to the pathological diagnosis; in the histopathological findings: a diffuse gliosis degenerating into a glioblastoma multiforme; and in the light cast on the structural basis of emotion. The case is like an experiment designed by nature to support Papez's view of the mechanism of emotions.

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THE EPILEPTIC THRESHOLD IN SCHIZOPHRENIA

BY

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From time to time in the history of psychiatry attention has been centred on the relationship between epilepsy and schizophrenia. The views held on this subject seem to have moved through three distinct phases, like a Hegelian dialectical triad of thesis, antithesis, and synthesis. The first phase was characterized by a purely descriptive approach. Kraepelin (1910) noticed the occurrence of epileptic phenomena in 18% of his schizophrenics. Other observers have recorded figures of from 0·33% (Strauss) to 8·6% (Giese). In the absence of agreement about the incidence of these phenomena, the existence of the two conditions in one patient was presumed to be coincidental.

The second phase is best illustrated by the writings of Müller (1930) and Krapf (1929), who doubted whether the phenomena observed by the previous authors were due to idiopathic epilepsy and showed that cases reported as such in the literature were probably symptomatic epilepsies due to some coincidental pathology. They believed that a " relationship " of mutual exclusiveness existed, the constitutional basis of the two disorders being at opposite poles. A modification of this view led Meduna (1937) to try the induction of fits in the treatment of schizophrenia : he had noticed the remission that often occurred after spontaneous fits. While Meduna's trials led to one of the most spectacular advances in psychiatric therapy, the fact that the treatment proved far more valuable in conditions other than schizophrenia allowed the discussion of " schizophrenia and epilepsy " to recede into the background.

The third phase came with the advance of diagnostic methods in relation to epilepsy, and particularly with the introduction of the electroencephalogram (E.E.G.). The literature of this epoch was summarized by Hill (1948) who himself contributed important observations. Some writers, for example Hoch (1943), upheld the original Kraepelinian view of " total independence " ; Hoch did not publish any electroencephalographic studies of his own, but arrived at his conclusions by analysing reports in the literature. Others, notably Jasper, Fitzpatrick, and Solomon (1939), Gibbs, Gibbs, and Lennox (1938), and Davis (1940), found that epileptic types of electroencephalographic changes were more common in schizophrenia than chance would lead one to expect, and came to the conclusion that a chance relationship could not account for the occurrence of epileptic fits in schizophrenia. These workers believe that there is a positive relationship between the conditions of epilepsy and schizophrenia ; its exact nature is as yet incompletely understood, and observations so far made invite further investigations.

The use of the E.E.G. made the diagnosis of epilepsy more precise in certain ways ; for example, by the localization of discharging foci and the recognition of epileptic patterns in the periods between fits. It showed that when normal individuals are convulsed the electrical brain patterns are in no way different from those of epileptics with similar convulsions. That is to say, the tendency to epileptic discharges or to epileptic dysrhythmia is a property, under certain conditions, of all types of brain.

It has become common practice to study the E.E.G. under conditions of physiological change produced by over-breathing, lowering the blood sugar level either by starvation or insulin injection, the use of convulsants, the action of flickering light on the retina, etc. All these methods give a measurement of the stimulus required to make the brain discharge in an epileptic fashion. This is called the " threshold value " and can be stated in terms of the particular stimulus required in a particular individual to provoke an epileptic change in the E.E.G. A low threshold is considered to indicate a tendency to convulse easily.

These new methods change the whole question, for the main problem no longer depends on the association between schizophrenia and fits, but rather on whether there are in epilepsy and schizophrenia either some common or some mutually antagonistic neurophysiological mechanisms. This

in turn merges into the wider problem of the somatic changes in schizophrenia.

We are reporting elsewhere (Leiberman and Hoenig, 1953; Leiberman, Hoenig, and Hacker, 1953) a study of schizophrenics and epileptics, using the concept of the metrazol-flicker-threshold developed by Gastaut and Hunter (1950). The present investigation arose from observation of patients undergoing insulin coma therapy. We became aware of the frequent occurrence of muscular twitching, myoclonic jerking, and actual convulsions, which are now all recognized as the clinical accompaniments of " epileptic " discharges in the E.E.G., and it appeared, moreover, that the patients who regularly showed these phenomena recovered more frequently than those who did not. In a sense, the insulin was being used as a provocative agent, though the problem was being approached in an indirect way.

Material

The patients whose case histories were studied were all in-patients in the Bethlem Royal Hospital and Maudsley Hospital, and had " deep insulin therapy " between January, 1947, and December, 1951. The total number investigated was 304, which did not include patients in whom the treatment was interrupted prematurely because of death, irreversible coma, gangrene, intercurrent illness, or a patient's refusal to continue.

According to the immediate outcome of the treatment, the patients fell into three groups: recovered, 87 (28·6%); improved, 121 (39·8%); and not improved, 96 (31·6%).

In all these patients the diagnosis of schizophrenia had been made before treatment was started. Since not all schizophrenics are treated by deep insulin, this is only a fraction of all patients admitted to the joint hospital with a diagnosis of schizophrenia during the years under investigation.

The age of the patients ranged from 7 years to 46. By far the largest number fell between the ages of 20 and 30, the average being about 27 years. The average age in each group was nearly the same, although the range differed somewhat: recovered, 27·3 years, ranging from 17 to 40; improved, 28·2 years, ranging from 15 to 46; and not improved, 25·5 years, ranging from 7 to 46. Details of age distribution in relation to the outcome of treatment are discussed below.

The average number of " treatment days " of the insulin coma therapy was 52·3 days for the " recovered " group, 50·8 days for the " improved " group, and 53·7 days for the " not improved " group; the differences are not significant. The average number of comas in each group was: recovered, 33·8; improved, 35·3; and not improved 33·6. Again the differences are insignificant.

Methods

The information analysed in this report was taken from case records only, the diagnosis being made always by the physician in charge of the patient and entered clearly on the front sheet of the case records. Often the diagnosis was more specific, giving the type of schizophrenia, e.g. catatonia, hebephrenia, but as this was not done in all cases no attempt has been made to keep the diagnostic subgroups separate.

On the front sheet is also entered the outcome of the treatment. From 1949 onwards this was stated under the six headings shown below, but in order to simplify we classified the outcome in three groups, namely: (I) recovered (which corresponds to 1), (II) improved (which corresponds to 2–4), and (III) not improved (which corresponds to 5–6).

Original Classification in Case Records	Our Classification
(1) Recovered	(I) Recovered
(2) Much improved (3) Improved (4) Slightly improved	(II) Improved
(5) No change (6) Worse	(III) Not improved

We further examined the records of the actual insulin treatment, which are filled in each day by the nurse who supervises the treatment, and which give a variety of information. The occurrence of epileptic phenomena, i.e. twitchings or myoclonic jerks, is recorded in a special column headed " twitches " and is indicated by one or more crosses. Epileptic fits are also recorded separately. Since this investigation was not designed as an experiment, but is katamnesic in nature, the entries by the nurses were " blind ".

The investigation consisted in counting the days on which epileptic phenomena, such as " twitches ", myoclonus, or fits, occurred in the course of the treatment, and expressing them in a percentage of the total number of treatment days. Thus if phenomena occurred in 10 days out of a total of 50 days the figure would be 20%. Grouping the patients into the three groups of " recovered ", " improved ", and " not improved ", the averages of these percentages in the different groups were compared.

Results

The results are tabulated in Tables I and II. The averages in Groups II and III are similar, although the " improved " group persistently shows a slightly but insignificantly higher average than the

TABLE I

NUMBER OF DAYS ON WHICH "EPILEPTIC" PHENOMENA OCCURRED* DURING INSULIN COMA THERAPY, AS PERCENTAGES OF TOTAL NUMBER OF TREATMENT DAYS

Treatment Year	No. of Days when Epileptic Phenomena Occurred			II+III Not Recovered
	I Recovered	II Improved	III Not Improved	
1947	33·1	19·3	17·1	18·1
1948	43·8	29·5	25·1	27·9
1949	54·2	33	25·3	30
1950	40·9	28·7	23·3	28
1951	39·5	26·4	20·4	23·6
Total	41·17	27·83	22·95	25·67

*The figures were worked out for each patient and averaged.

TABLE II

THE INCIDENCE OF EPILEPTIFORM FITS IN THE COURSE OF TREATMENT

	Recovered		Improved		Not Improved	
	Total No. of Patients	No. of Patients with Fits	Total No. of Patients	No. of Patients with Fits	Total No. of Patients	No. of Patients with Fits
Total	87	33	121	38	96	14
Percentage	37·9		31·4		14·6	

"not-improved" group (Fig. 1). Groups II and III were therefore made into one group, the "not recovered" group; this group differs from the "recovered" group persistently year by year, and the difference is statistically significant.

Table I shows clearly that in those patients who recovered after deep insulin therapy epileptic phenomena, such as myoclonic jerks or fits, occurred more frequently than in those who did not recover.

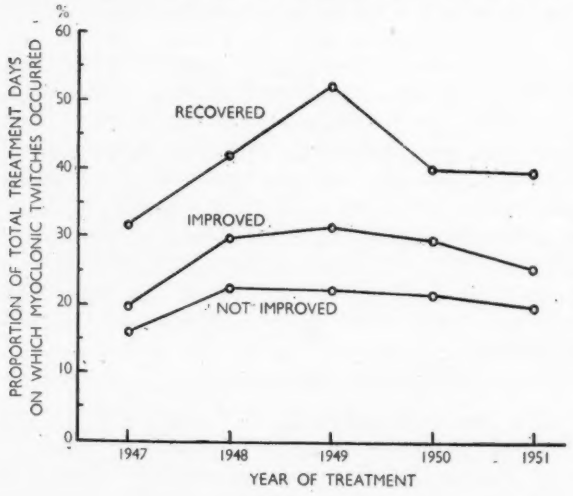

FIG. 1

Table II shows the occurrence of fits only in relation to short-term prognosis. No notice was taken of the number of fits each patient had, but only of the occurrence or absence of fits as such. The difference between the groups is again striking and on statistical examination is shown to be significant.

Discussion

There are various possible sources of error in the observations which may affect these results. In a busy insulin unit some at least of the minor manifestations of twitching or myoclonus are likely to be missed, though one can be certain that all fits are recorded. Again, it is well recognized that persistent myoclonus is often the precursor of a fit, and patients who jerk habitually often receive some anticonvulsant medication which can effectively suppress both the jerking and the possibility of a fit. No allowance has been made for patients receiving regular anticonvulsants. Both these errors, however, would tend to mask the significance of the results, so that if, in spite of them, a general tendency shows, it is likely to be significant.

The duration of the epileptic activity may be significant in relation to the prognosis, but it was impossible to estimate this from the records available.

The patients themselves were a special group, selected for insulin treatment on the basis of favourable prognostic signs and symptoms, such as short duration of illness, floridity of symptoms, acute onset, etc. Moreover in a certain number of cases the diagnosis may have been problematic. These factors, however, do not affect the significance of epileptic phenomena in relation to prognosis.

A comparison was made between our results and the results of a three-year follow-up study of untreated schizophrenic patients discharged from the Maudsley Hospital in 1934 and 1935 (Guttmann, Mayer-Gross, and Slater, 1939). Guttmann and his colleagues used different categories in the classification of their results, but their "total recovery" group would seem to be comparable with the "recovered" group in the present investigation. We can therefore compare their figure of 21·5% recovered with the figure of 28·6% recovered in the present investigation. The results in the present series are biased, of course, since the patients were a selected group; also, in the present study the immediate outcome, not the three-year follow-up results, was used. Allowing for this bias, however, the difference is very small (7·1%).

We could not find any reports in the literature with which to compare our general findings on the

relation of epileptic phenomena to prognosis. The significance of epileptic fits alone has from time to time been investigated, generally with inconclusive results, and in a recent statistical study Cohen (1951) found no correlation between short-term prognosis and the occurrence of fits. It is therefore interesting that we could find a significant difference between the prognostic groups in relation to fits.

While it would appear from our findings that a patient who shows much epileptic activity during insulin treatment has a good prognosis, the relationship is not an absolute one ; not every patient who has such a high incidence is going to recover, nor is the opposite the case. In attempting to analyse exceptions, no constant factor was found that could be held generally responsible. Some of the " not recovered " patients with much epileptic activity had a history of head injury, some showed epileptic E.E.G.s before insulin therapy was started. Brain damage was not a frequent factor in these patients' histories, however, and had sometimes occurred in patients with little epileptic activity, some of whom had abnormal E.E.G.s. These findings appear contradictory, and in addition cannot be properly evaluated as only a minority had had electroencephalographic tests before treatment.

The age distribution for the different groups is shown in Table III, the average age in each group

TABLE III
THE AGE DISTRIBUTION OF THE PATIENTS

	Age Range					
	–20	21–25	26–30	31–35	36–40	41–
Recovered	14*	26	22	13	9	3
Improved	21	29	27	21	13	10
Not improved ..	27	18	32	6	10	3

*The figures represent the number of patients in a particular age range.

being roughly the same. Whereas in the " recovered " and " improved " groups the curves are approximately normal, in the " not improved " group the curve shows three peaks, one in the youngest and one in the oldest range, in addition to the one in the middle range. This might be expected, since it is known that the prognosis is worse for the young and the old than for the middle range.

One can consider myoclonic jerks, fits, etc. during insulin therapy as analogous to the " threshold " phenomena mentioned at the beginning of this paper. Assuming that those patients exhibiting epileptic phenomena under insulin were more easily excitable, i.e. would have a lower threshold, one would expect to find an inverse relation between the dose of insulin, on the one hand, and epileptic phenomena and prognosis on the other. As will be seen from Table IV, however, the average dosages of insulin were not significantly different in the three groups.

TABLE IV
AVERAGE NUMBER OF INSULIN UNITS GIVEN DAILY DURING TREATMENT

Treatment Year	Average No. of Insulin Units Daily		
	Recovered	Improved	Not Improved
1948	200	235	152
1949	289	223	251
1950	231	221	242

The " threshold " may, of course, be related to blood sugar level rather than to insulin dosage. To infer directly the blood sugar level from the amount of insulin injected would generally be inadmissible, and particularly so in schizophrenic patients who are known to respond abnormally to insulin and who are often found to be " insulin resistant ".

Finally it is possible that the short-term result of treatment depends on the depth of the metabolic change induced by insulin, and that the epileptic phenomena are simply an indicator of the degree of such a change. The aim during treatment is to reach coma level, and a certain safe depth is produced in each patient. It can be assumed that the metabolic change is similar in each patient. It can be assumed that the metabolic change is similar in all cases where coma is reached. Since there was no significant difference between the groups in the average number of comas per patient, the average dose of insulin per patient, or the depth of coma aimed at, we may assume that the metabolic change in the subjects in each group was similar in degree.

Conclusions

The most obvious explanation of these findings would be that the therapeutic effect of deep insulin treatment is due to the production of these epileptic phenomena. There is enough evidence from other fields of the direct therapeutic action of induced epileptic phenomena to suggest such a view.

There is, however, another possibility. When the insulin treatment results are compared with the spontaneous recovery rate in an untreated group of schizophrenics it has been shown that the two groups are not very different. The comparison to be exact would of course require a more detailed analysis than we were able to carry out, but even

although the conclusion must be regarded as approximate only, it would seem that the more frequent appearance of epileptic phenomena after the administration of insulin is simply a characteristic of the group who recover.

A further theory which might help to explain our findings is Hill's (1948, 1950) suggestion that the relation between the epileptic threshold and the schizophrenic state is a changeable one, and is not constant in one patient at all times or at different stages of his illness. There is a dynamic interplay between the tendency to induced epileptic phenomena on the one hand and the stage of the illness on the other, so that the threshold falls as the illness nears its end. Hill suggests that this changing threshold is evidence of the functioning of a homeostatic mechanism, which brings about a restitution of the " normal balance " of the central nervous system.

More evidence has appeared than that quoted by Hill to support such a view. Corriol and Bert (1950) have shown the changes in the metrazol-flicker threshold in the course of a catatonic illness. We also intend to report a similar investigation elsewhere. It is therefore possible that the lowered threshold of the " recovered " group is due to the illness being already near its end when insulin therapy was started. If this is so, then it might be possible to regard a low insulin, or possibly metrazol-flicker, threshold as a sign of a good short-term prognosis in schizophrenia, and to elaborate the insulin threshold or some similar procedure into a short-term prognostic test.

Summary

The case records of 304 schizophrenic patients, who received deep insulin therapy, have been examined.

A method was evolved to assess indirectly and approximately the amount of epileptic activity during coma therapy. This consisted in counting the days on which epileptic phenomena occurred during treatment and expressing them in percentages of the total number of treatment days.

The average of these figures is significantly higher in the group of patients who recovered than in those who did not.

An explanation of these findings is offered.

We wish to thank Dr. D. Hill for his help and encouragement. Mr. A. S. C. Ehrenberg gave advice on statistical problems.

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DISTURBANCES OF OCULOMOTOR FUNCTION ACCOMPANYING EXTRADURAL HAEMORRHAGE

BY

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That the state of the pupils provides an important clue to lesions developing at the base of the brain has been known for a long time, and there are few accounts in the literature devoted to extradural haemorrhage which do not contain a reference to the diagnostic significance of the pupillary signs associated with this condition. A review of the literature, however, indicates that information is incomplete or contradictory on the following points. (1) The precise time-sequence of the changes in both pupils and the significance which is attached to these: these changes were regarded by earlier writers as of considerable diagnostic significance though they were unaware of the factors responsible for them. In more recent times, however, there has been a tendency to emphasize the final phase of the process, as represented by bilateral dilated fixed pupils, and to neglect the sequence of events which leads up to it. (2) Whether the signs of third nerve involvement are central, nuclear, or peripheral in origin. (3) The mechanism by which oculomotor function is disturbed. (4) Whether or not function is also impaired or lost in the field served by the somatic motor fibres of the oculomotor nerve and if so whether these changes precede, follow, or develop simultaneously with those due to involvement of the pupillo-constrictor component. This introduces the question of the relative susceptibility of the various fibres, somatic, motor, and pupillo-constrictor, to mechanical deformation and whether such differential susceptibility, if it exists, is to be accounted for on the basis that some fibres are physiologically more sensitive or anatomically less well protected. This feature has assumed significance in view of a recent observation (Sunderland and Hughes, 1946) which indicates a relative concentration of the pupillo-constrictor fibres in the upper sector of the oculomotor nerve. (5) In the event of conduction being blocked in all fibres, the rate and order in which different fibres recover following relief from mechanical distortion.

The object of this paper is to report the results of an investigation undertaken to answer these questions. During the course of the enquiry other interesting points have emerged. Incidentally, we are not concerned with disturbances of oculomotor function which immediately follow injuries of the orbital contents or of the third nerve in the form of a tearing or avulsion of its fibres, or of haemorrhage into its nucleus in the mid-brain. The type of disturbance under review concerns secondary involvement of the nerve arising from complications as a result of the injury which lead to the gradual development of signs some time after the accident, often as the patient is becoming increasingly comatose.

Material

The account of the normal anatomy of the oculomotor nerve is based on the examination of more than 100 cadavers, and the distortion which occurs at the base of the brain following cerebral shift and tentorial herniation has been investigated in nine necropsy specimens, four of which were the result of an extradural haemorrhage. The necropsy material permitted a reconstruction of the events which follow the development of these complications. Observations were also made on nine cases of extradural haemorrhage in which the pupillary changes and eye movements were followed in as great detail as was practicable. In a further 16 cases hospital records were consulted; in general these were incomplete but some information was provided by each. There is no need to elaborate the difficulties of carrying out repeated observations on a critically injured person and of testing eye movements in the unconscious individual. For these reasons some of our own records are inevitably incomplete.

In four of the patients who died the brain was obtained at necropsy in a state which permitted a study of the manner in which the pupillary signs had been produced.

Normal Anatomy

The oculomotor nerve emerges from a sulcus on the medial aspect of the cerebral peduncle and passes forwards and laterally to skirt the lateral margin of the posterior clinoid process. The nerve then passes on to, and courses along, the roof of the cavernous sinus for a short distance before entering the lateral wall of that structure. Between the brain stem and the posterior clinoid process the nerve is crossing the interval bounded by the margin of the tentorial notch laterally, the dorsum sellae anteriorly, and the brain stem posteriorly. This interval will be called the tentorial gap.

As it crosses this space the nerve has certain important vascular and cerebral relations (Figs. 1, 2, 3, and 4). Superior relations are the posterior communicating and posterior cerebral arteries ; the latter crosses the nerve on its way laterally. The superior cerebellar artery runs beneath the nerve as it travels laterally to pass beneath the tentorium. A portion of the uncal region of the temporal lobe normally extends inwards over the margin of the tentorium and into the tentorial gap ; in doing so it becomes closely related, supero-laterally, to the third nerve. It should be emphasized that this portion of the temporal lobe is, in the majority of cases, a normal content of the tentorial gap and a customary superior relation of the third nerve.

An earlier investigation has shown that the pupillo-constrictor fibres are concentrated in the upper part of the nerve from the cavernous sinus to the mid-brain (Sunderland and Hughes, 1946). Thus two vessels, the posterior cerebral and the posterior communicating, and a portion of the temporal lobe are intimately related to that aspect of the third nerve in which the pupillo-constrictor fibres are concentrated.

Pathological Anatomy

As bleeding occurs into the extradural space the subjacent cerebral hemisphere is compressed in a general direction medially. As a result the cerebral tissue, which is normally related to the tentorial gap, is forced downwards through it into the posterior cranial fossa. Though several accounts are available of the manner in which tentorial herniations develop in a variety of supratentorial expanding lesions (Meyer, 1920 ; Kernohan and Woltman, 1929 ; Spatz and Stroescu, 1934 ; Vincent, David, and Thiébaut, 1936 ; van Gehuchten, 1937 ; Jefferson, 1938 ; Schwarz and Rosner, 1941 ; Evans and Scheinker, 1943 ; Scheinker, 1945), few of these refer to, or are concerned with, involvement of the third nerve and those that do omit significant details pertaining to the mechanism of this involvement and to the associated disturbances of function. Exceptions are the accounts by Dott (1939) and Reid and Cone (1939).

On the side of the lesion the herniated mass is, in the initial stages, forced on to the upper surface of the third nerve which is crossing the gap beneath it, while the posterior cerebral artery, which is intervening between the two, deforms both and may subsequently be compressed between them (Figs. 5 and 6). The superior portion of the nerve is the first to be affected, and, since the pupillo-constrictor fibres are concentrated in this region, early changes in the pupil on the affected side would be expected. Further complications develop as the supratentorial pressure increases.

That portion of the uncal region of the temporal pole which is overhanging the tentorial gap on the contralateral side may be forced on to and may compress the subjacent oculomotor nerve. Further development of the herniation on this side is usually prevented, however, because of the manner in which the herniation on the ipsilateral side comes to occupy the tentorial gap (vide infra).

The mid-brain is compressed both to the opposite side and backwards as the herniation on the ipsilateral side increases. The cerebral peduncle on the involved side assumes a more vertical direction than that on the opposite side, which is driven against the free edge of the tentorium (Figs. 7, 8, and 9). As a result of this displacement the ipsilateral third nerve comes to run more acutely laterally, is stretched, and is pulled more firmly into contact with the posterior clinoid process. The nerve on the opposite side, on the other hand, comes to run almost directly forwards and is slackened. This feature is illustrated in Figs. 7, 8, and 9. All the fibres comprising the ipsilateral third nerve are now involved and the deformation is such that the pupillo-constrictor fibres would have ceased to conduct.

As the infratentorial cerebral mass continues to increase in size it ultimately reaches and impinges upon the upper surface of the pons on the same side. The pons is tilted downwards, the descent being facilitated by the elongation of the mid-brain which follows its lateral compression. Two factors which further embarrass conduction in the third nerve are introduced by this movement. (1) Each third nerve is stretched because the site of origin from the medial aspect of the cerebral peduncle descends. (2) The basilar artery, which is tethered to the surface of the pons by numerous, short, transversely directed pontine branches, moves distally with the pons and with it the origin of each posterior cerebral branch. As a result each artery must ascend more

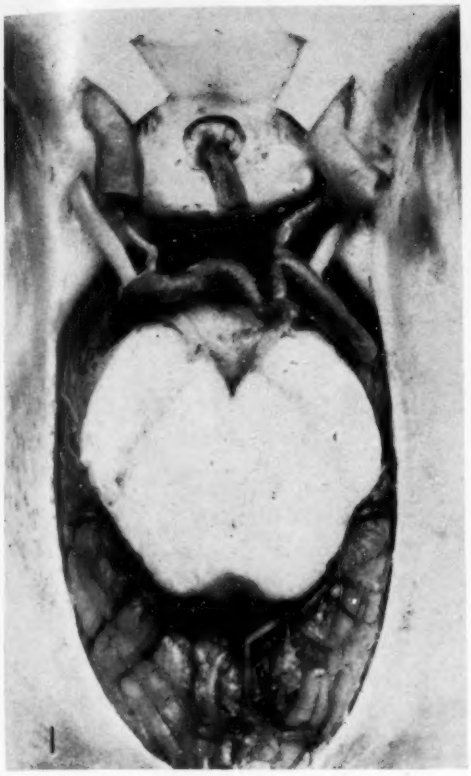

FIG. 1.—The base of the skull, viewed from above, in the region about the pituitary fossa, the cavernous sinus, and the tentorial notch. The manner in which the third nerve crosses the tentorial gap and is related to the posterior cerebral artery, the posterior communicating artery and the roof of the cavernous sinus is shown.

FIG. 2.—The region illustrated in Fig. 1 viewed from the lateral aspect to demonstrate the course of the third nerve across the tentorial gap as it passes between the posterior cerebral and superior cerebellar arteries.

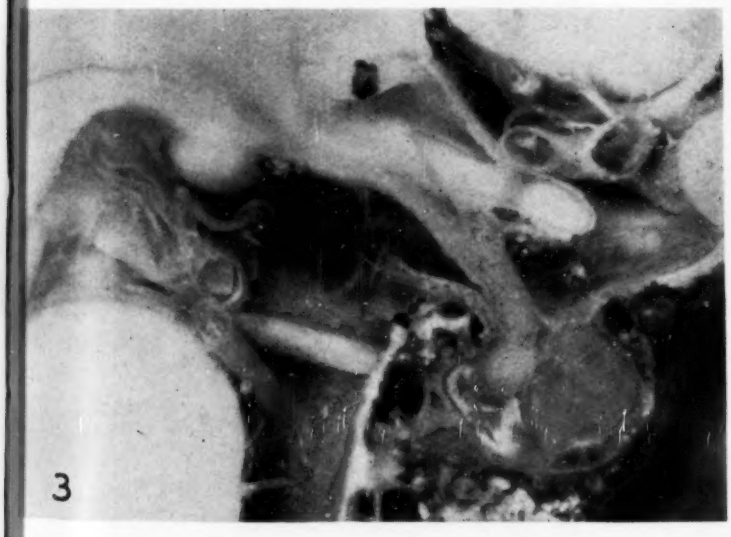

FIG. 3.—A mid-sagittal section of the base of the brain and the base of the skull illustrating how the third nerve crosses the tentorial gap and the manner in which it is sandwiched between the posterior cerebral and superior cerebellar arteries.

FIG. 4.—Basal aspect of the brain illustrating the boundaries and contents of the interpeduncular fossa. The stump of the third nerve is seen directed outwards and forwards between the posterior cerebral and superior cerebellar arteries. The posterior communicating artery is shown above and medial to the nerve. The indentation made in the temporal lobe by the free margin of the tentorium is clearly shown, as well as that portion of the uncus which bulges over the tentorial margin into the tentorial gap. The third nerve is seen to be a direct inferior relation of the uncal bulge as it passes forwards and outwards.

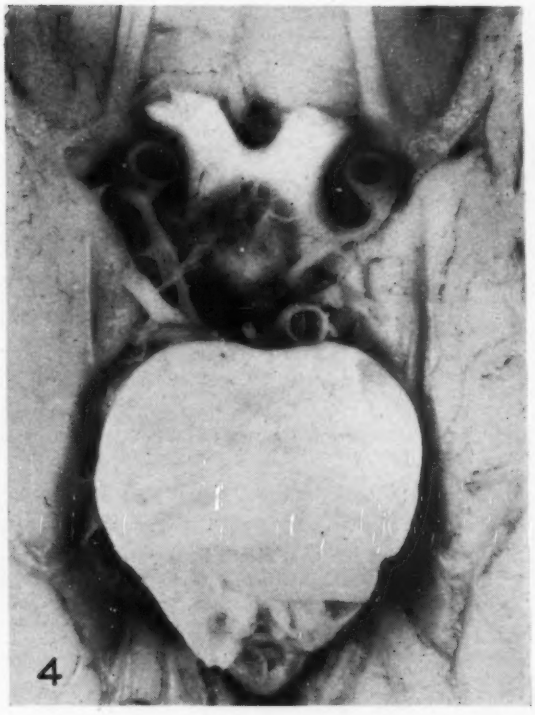

FIG. 5A.—Example of a tentorial herniation on the right side which has forced the posterior cerebral artery into the upper surface of the underlying third nerve. The artery has been reflected in order to expose the impression left on the upper surface of the nerve.

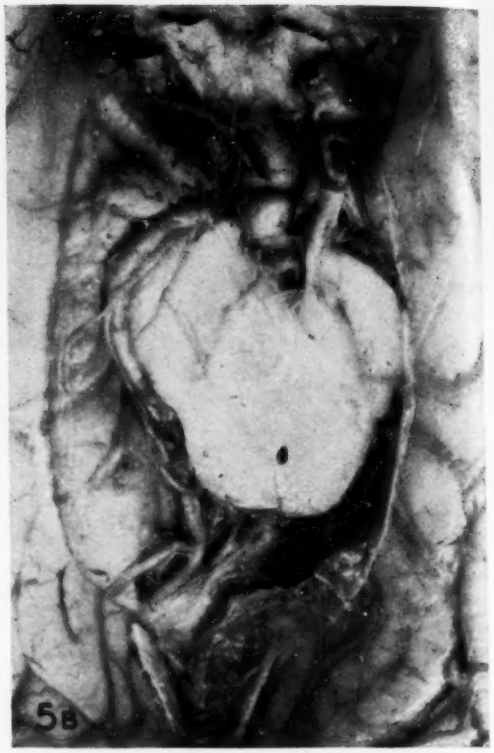

FIG. 5B.—The basal view of the brain corresponding to the arrangement at the base of the skull illustrated in A. The extent of the tentorial herniation on the side of the lesion is shown. On the under surface of the anterior portion of the herniation is shown the deep groove outlined and occupied by the third nerve as the herniated tissue was forced down upon it. The distortion of the opposite cerebral peduncle is well shown in comparison with the arrangement on the side of the herniation.

FIG. 6A.—The under surface of the brain in the region of the interpeduncular fossa in a specimen of tentorial herniation which illustrates the manner in which the posterior cerebral artery has deformed the herniated portion of the temporal lobe and the third nerve.

FIG. 6B.—The nerve has been displaced away from the artery to reveal the extent of the deformation.

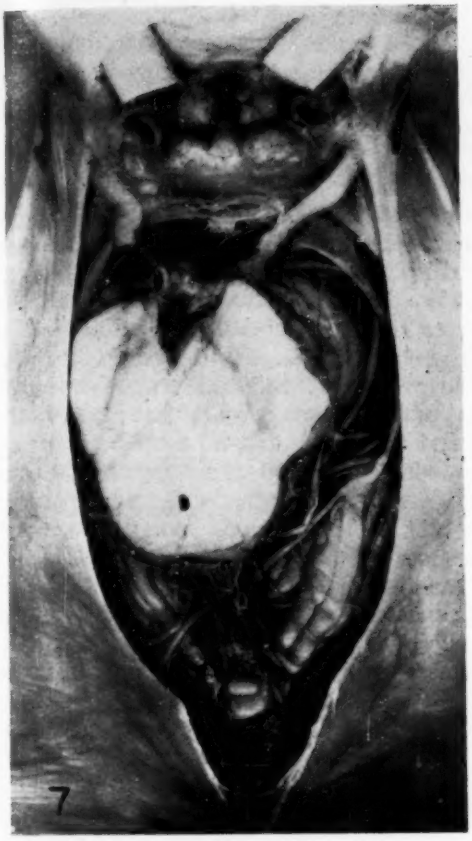

FIG. 7

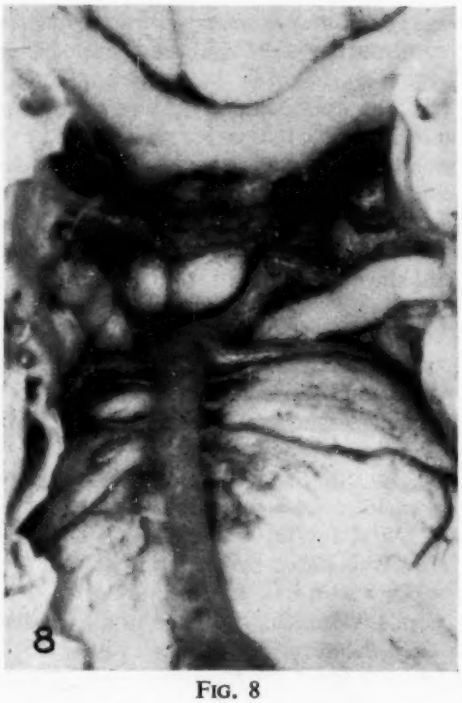

FIG. 8

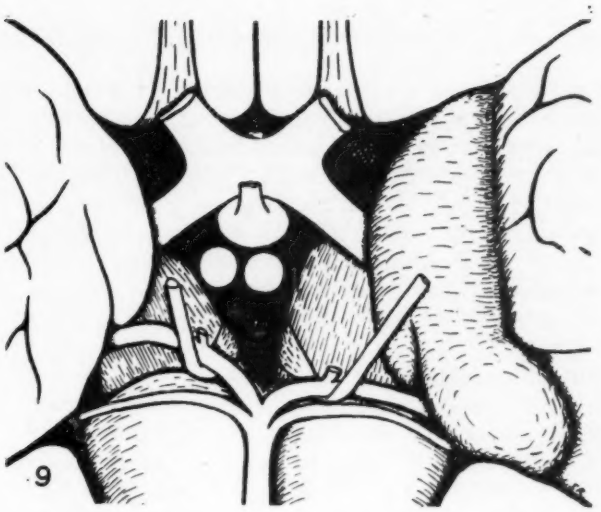

FIG. 9.—The interpeduncular region in a case of extradural haemorrhage with a tentorial herniation. The region has been exposed to illustrate some of the consequences of the herniation : (1) the angulation of each third nerve produced as it first descends to pass beneath the posterior cerebral artery ; (2) the alteration in the course taken by each third nerve as it passes towards the cavernous sinus ; (3) the displacement of the ipsilateral cerebral peduncle and interpeduncular structures e.g., the mammillary bodies ; (4) the impingement of the herniated cerebral mass on the pons which is deflected downwards, particularly on the ipsilateral side.

acutely in the initial part of its course in order to reach a supratentorial position, and in doing so each is pulled across and kinks the upper surface of the corresponding third nerve which has moved only slightly downwards at its origin. The final arrangement in the necropsy material was one in which the oculomotor nerves passed acutely *downwards* from their origin to reach the under surface of the corresponding posterior cerebral artery before turning acutely upwards, and then forwards and outwards towards the posterior clinoid process ; the angle of kinking produced in this way varied from 90° to 100° (Fig. 9). The compression and angulation of

FIG. 7.—The arrangement of the parts in the region of the hiatus of the tentorium in a case of right-sided tentorial herniation. The brain stem has been deflected to the left and the left cerebral peduncle compressed against the free edge of the tentorium. As a result of this displacement the origin of the right third nerve has moved to the left and the nerve now runs more acutely outwards and forwards. The origin of the left nerve, however, has been displaced so that it is now closer to, and more directly behind, the posterior clinoid process on that side. As a result the nerve is slackened. The stretching of the ipsilateral nerve and the slackening of the contralateral are well shown. (The origin of the left third nerve from the brain stem was unfortunately destroyed during the removal of the brain.)

FIG. 8.—Basal view of the brain in a case of tentorial herniation illustrating the displacement of the interpeduncular structures (e.g. mammillary bodies) to the contralateral side. The difference in the angle of inclination of the two third nerves is clearly shown as is the stretching on the ipsilateral and the slackening on the contralateral side. Also well shown is the manner in which the contralateral third nerve is forced into the angle of divergence of the posterior cerebral and superior cerebellar arteries as a result of the displacement brought about by the herniation.

the nerve thus produced was particularly marked on the ipsilateral side where the pons and artery were displaced further distally owing to the tilting of the former. It should be noted, however, that the superior aspect of the contralateral third nerve is finally involved as the result of such gross displacement. Furthermore the lateral displacement described above could also be responsible for wedging the contralateral nerve more securely into the angle outlined by the diverging posterior cerebral and superior cerebellar arteries (Fig. 8).

Lastly as the supratentorial pressure increases, the brain stem is compressed and this results first in narrowing of the aqueduct of Sylvius, obstruction of the flow of the cerebrospinal fluid, and a further rise in the supratentorial pressure. A vicious circle is thereby introduced in which the herniation aggravates those conditions which favour and accelerate its development. The second result is compression of the contralateral cerebral peduncle against the firm free edge of the tentorium. In this peduncle are descending the corticospinal fibres which are destined for the ipsilateral side. Involvement of these fibres leads to the appearance of signs of an upper motor neuron lesion on the same side as that on which the haemorrhage is occurring.

As the herniation continues to enlarge, the brain stem is slowly compressed until the aqueduct of Sylvius and the neighbouring vessels are obliterated and the vital functions are embarrassed and ultimately fail.

There may be some departures from this sequence of events but these are of a minor nature.

A study of our pathological material demonstrates that the third nerve is involved where it is slung across the tentorial gap and not where " it crosses the greater wing of the sphenoid bone " as has been described by Reid and Cone (1939). We also do not agree with the statement of Gurdjian (1938) that " the third nerve paralysis is brought about by pressure against the third nerve in its course through the superior orbital fissure ". Furthermore in the post-mortem specimens there was no other cerebral pathology which could have accounted for the disturbances of oculomotor function.

The findings indicate that the order of involvement of the fibres comprising the third nerves is as follows : (1) the superior portion of the ipsilateral nerve in which are concentrated the pupillo-constrictor fibres ; (2) the remainder of the ipsilateral nerve and hence its somatic motor fibres ; (3) the superior portion of the contralateral nerve and therefore the contralateral pupillo-constrictor fibres ; (4) the remainder of the contralateral nerve which represents the somatic component.

In this process the rate of development of the distortion is important but with extradural haemorrhage it usually occurs sufficiently rapidly to lead to the early appearance of signs of impaired conduction in the nerve.

Generalizations Based on Clinical Observations

The Behaviour of the Pupils.—The pupillary changes appeared early and progressed rapidly to the final phase when both pupils were fully dilated and fixed. Excluding two patients, who pursued a subacute course and failed to develop oculomotor signs, the first change was observed on the ipsilateral side in every case and was evident within seven hours of the injury ; in three patients it had appeared within the first hour. Both pupils were fully dilated and fixed approximately two to five hours *after the appearance of the pupillary changes*, though in one patient this condition was delayed for 12 hours.

An analysis of the data indicates that the pupillary changes developed in the following order :— First, the pupil on the affected side constricted ; this phase is apparently very short. In three patients the ipsilateral pupil was constricted when they were first examined three hours, three and a quarter hours, and three hours 35 minutes after the injury and the pupil was dilating when they were next examined 30, 20, and 45 minutes later respectively. In these cases the duration of the constriction before the initial examination could not be determined, but the sequence of events observed in the contralateral pupil confirms the belief that the phase of ipsilateral pupillary constriction is very brief. Thus, unless the patient is examined in the early stages and at very short intervals, the constriction would be missed. This could explain why it was not seen in the other cases and why so many have failed to observe it.

Secondly the pupil on the affected side slowly dilated and ultimately became fixed in full dilatation. The final stage was reached from one to seven and a half hours *after the injury* except in one case where eight to 13 hours elapsed before full dilatation occurred. Third, changes ultimately appeared in the contralateral pupil but sometimes began before the terminal stage was reached on the ipsilateral side. There was an initial constriction which persisted for the following periods : 10 to 30 minutes ; 10 to 55 minutes ; approximately 60 minutes ; and for less than one hour. This constriction was followed by dilatation so that approximately four and a half to 16 hours *after the injury* both pupils were fully dilated and fixed. It is emphasized, however, that the data indicate a rapid rather than a slow progression to full dilatation ;

in most cases both pupils were fully dilated and fixed within seven hours. Holman and Scott (1925) have also stressed " the rapidity with which pupillary dilatation may appear on one side and be followed after a brief interval by dilatation on the other side ".

State of the Pupils in Relation to Prognosis.—Eleven patients died immediately or shortly after decompression. The state of the pupils immediately preceding decompression and the influence of the latter on the former are listed in Table I. A study of these data indicates that bilateral fully dilated and fixed pupils is an ominous sign, particularly when it has existed for more than 30 minutes. Two patients with these signs did survive, but in them the condition had existed for less than 15 minutes. This demonstrates the importance of early recognition and treatment. In three of the 11 fatal cases the pupil on the involved side was fully dilated and fixed while the pupil on the contralateral side was not affected. Thus recovery does not necessarily follow decompression at a time when the pupillary changes are confined to one side. The behaviour of the pupils following decompression was a valuable prognostic sign. In the cases terminating fatally decompression had no effect on the state of the pupils except in two patients. In one the pupils had returned to normal 12 hours after operation ; death occurred five hours later. A necropsy could not be performed and death may not have been due to the complication which is believed to be responsible for the persistence of the pupillary signs. In the second there was a reduction in size following decompression but no recovery of the reaction to light. A necropsy revealed an unrelieved tentorial herniation.

On the other hand, in the surviving patients there was, with one exception, a rapid recovery of pupillary activity ; in the exceptional case recovery was delayed somewhat (Table II).

Behaviour of the Pupils after a Second Bleeding.—In two patients further bleeding occurred after a decompression which had been followed by recovery of the pupillo-constrictor mechanism. In one dilatation of the pupil on the affected side was observed two hours 40 minutes after the first operation ; it had not been present 60 minutes earlier. This pupil was fully dilated and fixed when next observed 30 minutes later at which time the contralateral pupil was enlarging. At this stage the wound was reopened. This resulted in the recovery of the contralateral pupil within a few minutes, but two hours elapsed before both pupils were equal in size and normal in appearance and reaction. In the second patient the pupils were equal and reacting two hours after the first decompression. Ninety minutes later the ipsilateral pupil was slightly larger than the contralateral and within 15 minutes it was fully dilated and fixed. A second decompression was performed 40 minutes later when the ipsilateral pupil was fully dilated and fixed and the contralateral was normal and reacting. Within two minutes of evacuating the clot the ipsilateral pupil

TABLE I
STATE OF PUPILS BEFORE AND AFTER DECOMPRESSION FOLLOWED BY DEATH

Patient	State of Pupils before Operation	State of Pupils after Operation
C. D.	Both fully dilated and fixed for approximately 60 minutes	No record
C. P.	Both fully dilated and fixed for an unspecified period	No record
E. K.	Both fully dilated and fixed for 30 minutes	Unchanged
L. G.	Both fully dilated and fixed for 30 minutes	Unchanged
H. R.	Both fully dilated and fixed for 50 minutes	Unchanged
B. I. B.	Ipsilateral fully dilated and fixed for six hours and the contralateral fully dilated and fixed for 30 to 60 minutes	Unchanged
W. M.	Both fully dilated and fixed when first seen four and a half hours after the injury	One and a half hours after operation slight reduction in size of both pupils which were not reacting to light ; eleven hours after operation pupils further reduced in diameter but not reacting ; remained in this state for three and a half days when both pupils suddenly dilated, first the ipsilateral pupil second the contralateral. Subtemporal decompression revealed a swollen brain. Operation followed by slow reduction in the size of both pupils over six to 10 hours. No reaction to light and the ipsilateral pupil remained larger than the contralateral. No further change and patient died six days later
R. C.	Ipsilateral dilated and fixed for at least 60 minutes ; contralateral dilating for 30 minutes	Unchanged
D. B.	Ipsilateral fully dilated and fixed	Ipsilateral unchanged ; contralateral fully dilated and fixed half an hour before death
J. F.	Ipsilateral fully dilated and fixed for 45 minutes	Pupils had returned to normal within 12 hours of decompression ; death five hours later
G. G.	Ipsilateral fully dilated and fixed for at least 90 minutes	Unchanged

began to react without altering in size. Two hours after the operation both pupils were normal in every respect. Thus the conditions and consequences of the second bleeding were almost identical in the two patients.

TABLE II
STATE OF PUPILS BEFORE AND AFTER DECOMPRESSION FOLLOWED BY RECOVERY

Patient	State of Pupils before Operation	State of Pupils after Operation
A. M.	Both fully dilated and fixed for 15 minutes (ipsilateral for 0 to three and three quarter hours, contralateral for 15 minutes)	Both equal and reacting when skull was being closed
W. H.	Both fully dilated and fixed for a few minutes (ipsilateral for one and a quarter to two hours, contralateral for a few minutes)	Both moderately dilated and reacting to light five to 13 minutes after decompression. Pupillo-constrictor fibres recovered gradually in next six hours, ipsilateral lagging slightly behind contralateral
L. F.	Ipsilateral fully dilated and fixed for 15 minutes; contralateral smaller and reacting	Within 10 minutes both equal in size, moderately dilated and reacting to light; 70 minutes later normal in their appearance and reactions; 2 hours 40 minutes after operation, slight dilatation of the ipsilateral pupil; 30 minutes later, ipsilateral pupil fully dilated and fixed and the contralateral dilating with slight reaction to light. Immediate decompression and within minutes contralateral pupil became reduced. Two hours after second operation both pupils equal in size and normal in appearance and reaction
A. C.	Ipsilateral fully dilated and fixed for at least two and a half hours; contralateral normal	Ipsilateral showed some recovery two hours later but still larger than contralateral 14 hours after operation
G. H.	Ipsilateral almost fuily dilated and fixed	No record
T. D.	Ipsilateral dilated for two and a half hours and fixed for approximately 30 minutes; contralateral normal and reacting	Both normal, equal in size and reacting two hours after operation; three and a half hours after operation, ipsilateral larger than contralateral with both reacting; 15 minutes later, ipsilateral dilated and fixed and contralateral small and reacting; 40 minutes later second decompression, when ipsilateral pupil dilated and fixed and contralateral constricted and reacting. Clot evacuated: within two minutes ipsilateral pupil began to react without altering in size; 80 minutes later both pupils reacting to light with ipsilateral slightly dilated; two hours after operation both pupils normal in size and reacting to light
M. K.	Ipsilateral fully dilated and fixed; contralateral not fully dilated but fixed for 20 to 90 minutes	One hour after evacuation of clot both pupils reduced in size, ipsilateral to two-thirds its dilated size and contralateral normal and reacting sluggishly; 11 hours after operation both pupils almost equal in size (ipsilateral slightly larger than contralateral); seven hours later both pupils equal in size and reacting to light

The rapidity of the recurrence of the pupillary signs in these patients was presumably due to some residual defect in the pupillo-constrictor fibres following the original decompression which rendered them more vulnerable to a second deformation. Such an explanation is supported by experimental evidence that it is easier to block conduction in peripheral nerves a short time after these have recovered from a compression block.

The Behaviour of the Extraocular Muscles.—Independent ocular movements could not be tested in the unconscious individual but observations on the size of the palpebral fissure when the eyes were open and the range of involuntary ocular movements indicated, in the cases investigated, that oculomotor function was affected on the ipsilateral side but not on the contralateral. This ipsilateral disturbance was confirmed when voluntary eye movements could be tested. The findings also indicate early involvement of the somatic component of the nerve. Signs of extraocular involvement, however, persisted for long periods after decompression. The pattern of recovery in five patients was as follows. The medial rectus began to function 29 hours after operation. Six hours later eye movements were full in range but there was a ptosis of the upper lid which did not clear until a further 40 to 60 hours had elapsed. Eye movements, with the exception of downward gaze, were well performed 22 hours after operation. Twenty-three hours later the upper lid was still ptosed while downward gaze, though full in range, was still weak. Eye movements were fully restored three and a half days after operation; the ptosis was still present the following day but could not be detected when the patient was next examined 19 days later. The somatic fibres were not functioning six days after decompression. Twelve days later there was some recovery of the superior and inferior recti but none in the medial. Seventeen days after operation function was good except for a residual ptosis. Recovery first appeared in the inferior rectus and was well advanced at 36 hours at which time function reappeared in the medial rectus. Four days later both were functioning normally, recovery having advanced more rapidly in the inferior than in the medial. On the other hand elevation of the eye and eyelid did not reappear until four and a half days later and a residual paresis was still evident a further 10 days later. The medial rectus began to function at two and a half days and was

functioning normally 24 hours later. Recovery in the remaining muscles was delayed for a further three days.

These observations indicate that recovery of the levator palpebrae superioris was delayed in comparison with the recti where the order of recovery varied but favoured the medial and inferior as opposed to the superior.

McKenzie (1938) reported a " varying degree of loss of movement of the eyeball " associated with the pupillary changes accompanying extradural haemorrhage, while Schwarz and Rosner (1941) refer, in passing, to " imbalances in extraocular muscles " associated with tentorial herniations complicating supratentorial tumours. In each case details were not provided. Reid and Cone (1939) have also described involvement of the extraocular muscles but it is not clear from their account whether the pupillary fibres succumbed first ; their data, however, suggest that recovery in the extraocular field was delayed in comparison.

Relative Susceptibility of the Pupillary and Somatic Components in the Oculomotor System.— We are unable to say whether the pupillo-constrictor fibres on the ipsilateral side fail before, at the same time, or later than the somatic fibres because when the patients were first examined signs of involvement of both were usually present. However, we are under the impression that the pupillo-constrictor component failed more rapidly and there is no doubt that this system was paralysed on the contralateral side when no disturbance could be detected in the corresponding somatic motor field. In those patients who survived the pupillo-constrictor fibres recovered rapidly, in some cases within a few minutes of the decompression, whereas the recovery of their somatic associates was delayed, for days in the case of the recti muscles and for weeks in the case of the levator palpebrae superioris, although in one patient the recovery of the recti was unduly delayed.

The general conclusion is that the pupillo-constrictor fibres are more susceptible to deformation, or to an associated impairment of their blood supply, than their somatic associates, and that following decompression they recover more rapidly. Furthermore there also appeared to be a relative susceptibility among the somatic fibres in that in some recovery was delayed in comparison with that in others. Whether they failed in any particular order could not be determined.

The Mechanism Responsible for the Pupillary Changes

Any explanation advanced to account for the occurrence of the pupillary changes associated with extradural haemorrhage must also explain the sequence of these changes, their bilateral incidence, their early appearance following the injury, and their prompt recovery on decompression, the involvement of somatic fibres on one side but not on the other, and why the pupils sometimes fail to recover on decompression, and why this is such an ominous sign.

As it develops, the hernia presses first on the upper surface of the third nerve on the same side where it is slung across the tentorial gap. Irritation of the subjacent fibres leads to constriction of the pupil because the pupillo-constrictor fibres are concentrated in the affected sector of the nerve. This phase, however, is usually short. Further bleeding leads to an enlargement of the herniation, further displacement of the parts, and further deformation of the nerve As a result conduction gradually fails in the pupillary fibres until paralysis is complete when the pupil will fully dilate and no longer react. While this is occurring the somatic fibres feel the effects of the compressing force and signs of impaired function appear in the extraocular muscles.

The appearance of signs on the opposite side indicates that the effects of the hernia are now being felt on that side. It has been shown that the hernia, as it enlarges, not only forces the brain stem to the opposite side, thereby driving the opposite cerebral peduncle against the tentorial edge, but that it impinges on the upper surface of the pons on the same side and forces that structure downwards. This leads to the descent of the basilar artery, and with it the origin of the posterior cerebral arteries. As a result each posterior cerebral artery is pulled into the upper surface of the nerve which is running beneath it. On the contralateral side this leads to irritation and later paralysis of the subjacent pupillo-constrictor fibres, and therefore to constriction followed by dilatation of the pupil. The somatic fibres in the contralateral third nerve escape because the mechanism responsible for deforming the nerve acts, initially, on its upper surface. If, however, the angular pull of the artery persisted the somatic fibres would ultimately be involved but before this occurred both pupils would be fully dilated and fixed and the somatic fibres on the ipsilateral side would have failed. This, however, is a condition which should be anticipated by the surgeon and prevented by surgery.

Following decompression and the rapid reduction of the herniation, the parts are relieved in the reverse order in which they were involved. The contralateral third nerve recovers first. On the affected side the pupillo-constrictor fibres recover

more rapidly than their somatic associates, presumably because the effects of compression on them are less lasting.

The Relative Susceptibility of the Different Fibres To Mechanical Deformation

The early signs of a pupillo-constrictor involvement on the same side followed by the occurrence of similar signs on the opposite side in the absence of extraocular disturbances suggests that the pupillo-constrictor fibres are more susceptible to mechanical deformation than are the somatic motor fibres. Is this due to the fact that the former are anatomically more exposed or to the fact that they are physiologically more sensitive ? The former explanation appears to be the more acceptable. The pupillo-constrictor fibres are concentrated in the upper part of the nerve and this is the first part to feel the effects of the deformation. Furthermore, if they were physiologically more sensitive to deformation it would be expected that, on release, they would recover more slowly. On the contrary, the pupillo-constrictor fibres recover rapidly whereas recovery in their somatic associates is long delayed.

It is believed that the fine fibres in peripheral nerves are less vulnerable to compression than the larger fibres. The findings of this investigation, however, do not conflict with this. The reason why the fine fibres in the oculomotor nerve fail so early is because they are anatomically more exposed. The findings also emphasize that in any consideration of relative susceptibility of nerve fibres to mechanical deformation anatomical features cannot be neglected.

Other Possible Mechanisms Responsible for the Pupillary Changes

In the preceding sections reasons have been given for attributing the oculomotor changes to involvement of the trunk of the nerve where it is slung across the tentorial gap. It remains to be considered whether the disturbances could be the result of changes initiated at central levels. Cairns (1929) inclined to the view that the pupillary dilatation results from cortical injury or disturbances of fibre tracts of the affected cerebral hemisphere. In the patients investigated by us the distribution of the clot, the absence of a cortical lesion in the cases examined at necropsy, and the pattern of the pupillary changes, particularly the reaction on the contralateral side, excluded a cortical origin for the disturbances.

Whether involvement of nuclear centres in the mid-brain is a contributing factor also requires consideration. However, the manner in which the tentorial herniation develops, the early appearance of pupillary signs confined to the ipsilateral side when mid-brain compression must be negligible, and the absence of somatic motor effects on the opposite side when the corresponding pupil is fully dilated do not favour such an explanation. It might be argued that the pupillo-constrictor centre in the third nerve nucleus is more sensitive to deformation, or ischaemia secondarily induced, than are the somatic components. However the nuclei (right and left) are so close together that it would be difficult to account for the progression of oculomotor signs on the basis of embarrassment of the third nerve nuclei. A nuclear origin for the disturbance has also been excluded by Reid and Cone (1939). This conclusion is consistent with the findings of Magoun, Atlas, Hare, and Ranson (1936) and of Crouch (1936) on the pupillary light reflex, while Bing (1939) describes the extraocular mechanism as suffering first in lesions of the mid-brain.

The herniation if unrelieved may proceed to impaction, and decompression is then without effect. Pressure on the nerves is unrelieved, the pupillary signs persist, and as the herniation continues to enlarge the brain stem is still further compressed, the vital functions are embarrassed and ultimately fail.

Cases of Extradural Haemorrhage not Associated with Impairment of Oculomotor Function

It is not to be concluded from this discussion that signs of impaired oculomotor function develop in all cases of extradural haemorrhage. Cases in which they fail to appear and in which the nature and site of the lesion are revealed by other signs are of course well known. There were two such cases in the series studied by us ; these were successfully treated by operation 53 hours and 12 days after the injury. Why the oculomotor mechanisms should be involved in some patients and not in others remains to be explained. The size of the clot alone is not necessarily a contributing factor. Thus in the case in which the diagnosis was not apparent for 53 hours the clot was as large or larger than that present in acute cases where pupillary signs appeared early. Individual variations in the rate of bleeding, in the development of a concomitant cerebral oedema and the extent to which this causes swelling of the brain, and in the arrangements of the parts at the tentorial notch are probably among the contributing factors. Nerves are more tolerant to slow than to rapid deformation. Again in some individuals the brain stem fits so snugly through the tentorial notch that little or no room is

available for the development of a hernia while in others, and these represent a majority, there is ample room.

The Significance of the Pupillary Changes

The appearance of pupillary signs following extradural haemorrhage is an indication that a highly dangerous state of affairs in the form of a tentorial herniation is developing.

The following points are emphasized in connexion with this complication.

The pupillary changes appear early and progress rapidly so that within approximately 12 hours of the injury both pupils will be fully dilated and fixed.

The pupillary signs appear first on the side of the lesion in the form of an initial constriction which is rapidly followed by dilatation. On the other hand, the contralateral pupil is not affected until the signs are well advanced on the ipsilateral side. We agree with Cock (1842), Hutchinson (1867-8, 1875-8), Jacobson (1886), Butler (1923), Holman and Scott (1925), Menninger (1927), Cairns (1929), Rand (1929), Blum (1931), Schörcher (1937), McKenzie (1938), and Woodhall, Devine, and Hart (1941) that a dilated fixed pupil is one of the most constant and reliable localizing signs.

Difficulty in localization arises when both pupils are fully dilated and fixed. At this stage, however, help may be obtained from a study of the involuntary ocular movements. The eye on the affected side is stationary whereas that on the opposite side is still roving because the somatic motor fibres on that side are the last to be involved and are only affected in the terminal stages.

The pattern of pupillary change provides a delicate indicator of the progress and extent of the herniation. The importance of the sequence of changes leading to fixed dilated pupils was recognized by the older writers, though they were unaware of the causative factors operating inside the cranium. In recent literature, however, there is a tendency to concentrate on the fixed dilated pupils and to neglect the sequence of events leading up to it. This is dangerous, for there is good reason for believing that by the time both pupils are fully dilated and fixed the tentorial complication is entering its terminal phases. Irreducible impaction is occurring and temporal decompression alone may then fail to correct the complication. The gravity of these extreme pupillary changes should be stressed. The findings of this enquiry suggest that the existence of fixed, dilated pupils for more than half an hour precludes recovery.

If the decompression is effective the pupillo-constrictor fibres recover rapidly. The pupils begin to contract and react within a few minutes of decompression.

Persistence of pupillary dilatation and the failure of the pupil to react to light after decompression is an ominous sign. An examination of the post-mortem material suggests that decompression in these cases has failed to relieve the herniation, probably because it was too long delayed. As a result the pressure on the nerves is unrelieved while obstruction of the aqueduct of Sylvius leads to a further rise in the supratentorial pressure which aggravates the herniation and ultimately leads to death.

The maximum time between paralysis of the pupillo-constrictor mechanism on both sides and decompression which is consistent with survival could not be ascertained but from the limited data at our disposal it appears to be very short (probably somewhere between three and 30 minutes). This emphasizes the importance of recognizing the herniation in the early stages of its development. In this connexion the behaviour of the pupils can be accepted as a delicate indicator of the changes occurring at the base of the brain.

It is obvious that a larger series of cases will need to be investigated before a critical point can be fixed after which decompression is no longer of avail. In any event individual variations can be expected since the rate of bleeding will vary from patient to patient. Our intention, however, is to emphasize the gravity of the ipsilateral dilated and fixed pupil and to stress that the urgency of surgery is to be measured in minutes rather than in hours.

The rapidity with which the pupillary changes develop and the significance attached to them makes accurate and repeated observations imperative until an extradural haemorrhage can be safely excluded.

Tentorial herniations develop as the result of a wide variety of expanding supratentorial lesions of which extradural haemorrhage is only one. Whether or not pupillary signs appear, depends on the rate at which the herniated mass increases in size and the nerve is distorted. Thus the herniation may develop so slowly that the nerve has time to accommodate itself to the changed conditions and no disturbance of conduction results until the condition is well established. On the other hand, pupillary changes appear early when the hernia develops rapidly, as in extradural haemorrhage which forms a semi-solid, space-occupying plaque. The rate of development of the pupillary signs is presumably influenced by the rate at which bleeding occurs in which individual variations are to be expected.

Summary

The disturbances of oculomotor function accompanying extradural haemorrhage have been investigated.

A study of pathological material demonstrates that (1) the disturbances of oculomotor function are due to deformation of the third nerve produced by the development of a tentorial herniation and the consequent displacement and distortion of the mid-brain, and (2) the site of the involvement is the trunk of the nerve where it is slung across the interval, the "tentorial gap", bounded by the margin of the tentorial notch laterally, the dorsum sellae anteriorly, and the brain stem posteriorly.

The manner in which the third nerves are involved, leading to the development of signs in the oculomotor field, is detailed.

Attention is directed to the pattern of pupillary change and to its diagnostic and prognostic significance. The behaviour of the pupils provides a delicate indicator of the changes occurring at the base of the brain.

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THE NOVEMBER (1952) ISSUE

The November (1952) issue contains the following papers :—

The Electrogram in Myopathy : Analysis with the Audio-frequency Spectrometer. By John N. Walton.

Thoracic Intervertebral Disc Prolapse with Spinal Cord Compression. By Valentine Logue.

Studies of Ischaemic and Post-ischaemic Paraesthesiae in Normal Subjects and in Sciatica. By John Marshall.

Three Cases of Achondroplasia with Neurological Complications. By John D. Spillane.

A Sex-linked Variant of Gargoylism. By Guy Millman and J. W. Whittick.

Electroencephalographic Studies in Cerebral Angioma. By D. P. Rosenberg.

Disorders of Perception and Performance in a Case of Right-sided Cerebral Thrombosis. By R. W. Gilliatt and R. T. C. Pratt.

Some Mechanisms of Tactile Localization Revealed by a Study of Leucotomized Patients. By Alick Elithorn, Malcolm F. Piercy, and Margaret A. Crosskey.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 12s. 6d.

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THE INTRA-ARTERIAL INJECTION OF NEOSTIGMINE AS A DIAGNOSTIC TEST IN MYASTHENIA GRAVIS

BY

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Harvey, Lilienthal, and Talbot (1941) and Harvey and Lilienthal (1941) reported that the effects of the injection of both acetyl choline and neostigmine into the brachial artery of patients with myasthenia gravis differed profoundly from those in the normal subject. Their results with acetyl choline could not be repeated by Wilson and Stoner (1947) or by Acheson, Langohr, and Stanbury (1948), but the intra-arterial injection of neostigmine is now recommended in standard textbooks as a diagnostic test for myasthenia gravis (Brain, 1951 ; Nattrass, 1952). Harvey and Lilienthal (1941) found that in all their cases of myasthenia gravis the power in the injected arm, which they imply was clinically myasthenic, improved after the injection, in contrast to the paralysis and fasciculation produced in the normal. The current theories of the pathogenesis of myasthenia gravis postulate an abnormal agent circulating in the blood, either with a curare-like action (Wilson and Stoner, 1944) or with the power to inhibit the synthesis of acetyl choline (Torda and Wolff, 1944). Presuming the existence of some such generalized metabolic defect, and despite the often extremely localized clinical manifestations of the disease, it would at least be reasonable to suppose that the intra-arterial neostigmine test might bring to light abnormalities in clinically unaffected muscles. It had come to our notice that the test was in fact being used in this way and that deductions as to the cause of oculomotor and bulbar palsies were being made from the response of clinically unaffected muscles to intra-arterial neostigmine. It was, therefore, decided to examine the results of such injections in myasthenic patients in whom the injected arm was affected and in those in whom it was not. As the paralysis produced in normal subjects has been presumed to be due to the accumulation of excessive amounts of acetyl choline, and therefore only quantitatively different from the response in myasthenia, the effects of graded doses were also studied in some of these patients.

Methods

Neostigmine methylsulphate was injected in doses of 0·25 to 1·5 mg. in a 0·25% solution, in all cases the initial dose being 1·0 mg. For subsequent injections the dose was reduced if paralysis had occurred with 1·0 mg. and increased if it had not. The injections were made with a tuberculin syringe and a hypodermic needle into the brachial artery at the elbow. The venous return from the arm was occluded with a sphygmomanometer cuff during the injection and for four minutes afterwards. During the actual injection the artery was occluded by digital compression immediately above the site of the injection. The release of the arterial flow on the completion of the injection ensured as far as possible the arrival of the neostigmine at the muscles in maximum concentration. The same arm was used throughout in each patient, and although no adverse effects on the vessel were observed, it was not thought justifiable to make more than two injections into the same artery. Both of us had gained considerable experience in the technique of the injection before the start of the present investigation, and no results are included in which there was doubt as to the injection being intra-arterial. Atropine, gr. 1/100 (0·6 mg.), was given subcutaneously 15 minutes before the injection.

The strength of the grip was measured on a mercury dynamometer before and at varying intervals after the injection. The possible effects on the grip of venous occlusion and of the discomfort of the arm-band were checked in each patient and were found to be negligible. When any doubt existed as to the clinical involvement of the injected arm the response of the grip to the subcutaneous injection of 2·0 mg. of neostigmine was recorded on a separate occasion.

Clinical Material

Ten patients were examined. In all the diagnosis of myasthenia gravis had been established by the usual clinical means and by the response to subcutaneous and oral neostigmine. In five patients signs of the disease were confined to the muscles supplied by the cranial nerves, while in the other five the injected arm was clinically myasthenic. All patients who were taking neostigmine omitted it before the test for as long as seemed to us safe.

Results

The results are shown in Table I. It can be seen that when the injected arm was not clinically myasthenic the intra-arteral injection of 1·0 mg. of neostigmine invariably produced great loss of strength of grip accompanied by coarse fasciculation. In contrast, when the arm was clinically myasthenic this effect never occurred but power either increased or showed no significant change. With smaller doses in patients without clinical myasthenia in the arm, there was either no change in power or a reduction of less degree than with 1·0 mg. In three patients in whom the injected arm was myasthenic 1·5 mg. produced an increase in power, although in one patient this increase was less than that produced by 1·0 mg. Fasciculation was never seen in this latter group of patients. The only adverse effect noted was a syncopal reaction in two patients. In both this occurred before the release of the sphygmomanometer cuff around the arm and therefore before the escape of any neostigmine into the general circulation. The effect must, therefore, have been due to the circumstances of the test and the insertion of the needle rather than to any pharmacological action.

TABLE I

PERCENTAGE CHANGE IN GRIPPING POWER AFTER NEOSTIGMINE IN WEAKENED AND UNAFFECTED ARMS OF MYASTHENICS

Case No.	Clinical Myasthenia of Injected Arm	Change in Gripping Power in Four Minutes of Venous Occlusion after Intra-arterial Injection (%)			
		Dose of Neostigmine (mg.)			
		0·25	0·5	1·0	1·5
1	Yes	—	—	0*	+35
2	Yes	—	—	0	+60
3	Yes	—	—	0	—
4	Yes	—	—	0	—
5	Yes	—	—	+66	+25
6	No	0	—	−100	—
7	No	0	—	−100	—
8	No	—	—	−90	—
9	No	−85	—	−100	—
10	No	—	−24	−75	—

* Changes of less than 20% are recorded as 0.

Discussion

As neostigmine is known to exert a direct action on muscle quite distinct from its anti-cholinesterase activity (Riker and Wescoe, 1946), it was not thought that these results would contribute to the controversy on the sensitivity of myasthenic muscle to acetyl choline (Harvey and Lilienthal, 1944; Wilson and Stoner, 1947). We have confirmed, however, that myasthenic muscle reacts to the same dose of intra-arterial neostigmine in a manner different to that of apparently normal muscle. An attempt to show that this was only a quantitative difference was not wholly successful. The inability to control the distribution of the injected dose between the skin and the muscles and between the individual muscles precludes any precise deductions, but it was shown that 0·25 mg. of neostigmine will not always produce paralysis in non-myasthenic muscle. We did not demonstrate the reverse, which we thought to be theoretically possible, the paralysis of myasthenic muscle with large doses of neostigmine, but the range of dosage was possibly not sufficiently wide. It is worth noting that in one myasthenic subject Harvey and Lilienthal (1941) produced transient fasciculation with the very large dose of 3·0 mg.

The conclusions with regard to the usefulness of the test in the diagnosis of myasthenia gravis are more definite. If the symptoms of the suspected case include weakness of the arms the test may be an aid to diagnosis, but unless the injected arm is clinically myasthenic the response will be that of normal muscle. As it is precisely in those cases in which there is weakness of muscles supplied by the cranial nerves alone that doubt about the diagnosis is most likely to arise, the usefulness of the test appears to be extremely limited.

Summary

Graded doses of neostigmine were injected into the brachial artery of five patients with myasthenia gravis in whom the injected arm was weak and of five in whom it was unaffected. In all the latter five patients the injection of 1·0 mg. caused great loss of strength of grip, while in the former strength increased or was unaffected.

Smaller doses in patients in whom the arm was not myasthenic sometimes failed to produce paralysis.

Paralysis of clinically myasthenic muscle was not produced with larger doses, but the range of dosage was small.

It is concluded that the intra-arterial injection of neostigmine does not assist in the diagnosis of myasthenia gravis unless the injected arm is itself weak.

It is with pleasure that we acknowledge the permission of Dr. F. R. Ferguson and Dr. G. E. Smyth to investigate and report on their patients.

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THE NEUROLOGICAL ASPECTS OF DERMATOMYOSITIS

BY

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Dermatomyositis is a descriptive title for a syndrome first recognized towards the end of the last century by Hepp (1887), Wagner (1887), and Unverricht (1891), and first described in this country by Gowers (1899). The clinical presentation of the condition is extremely variable and when its impact is chiefly on the muscles other muscular and nervous disorders may be simulated. With the exception of Oppenheim (1911), and to a lesser extent of Wilson (1940), dermatomyositis receives scant mention in textbooks of neurology and is seldom discussed in the differential diagnosis of bulbar palsy or of weakness or atrophy of the limbs. It is the purpose of this communication to describe three cases referred for neurological opinion illustrating points of diagnostic difficulty, and to review the subject from a neurological aspect. Some justification may be drawn from the remark of Keil (1940) that " neurologists seem to be hardly familiar with this particular condition ".

Case Reports

Case 1 : N. J. (206663).—A school teacher aged 61 was admitted to the Manchester Royal Infirmary under the care of Dr. F. R. Ferguson on February 9, 1951. She had originally been referred to a chest surgeon on account of persistent fluid at the base of the right lung following a chest infection 18 months earlier. It was noticed that her voice was weak and she also complained of dysphagia. Examination of the larynx showed diminished abduction of the vocal cords, and a barium swallow was thought to suggest a bulbar palsy ; the patient was therefore referred for neurological opinion.

The patient said that for the past nine months she had felt increasingly fatigued and weak and had had particular difficulty in preventing her head from dropping forward. Four months ago her voice had become weak and she volunteered the information that this was much more marked towards the end of the day when it became difficult to speak at all. Two months ago she began to have difficulty in swallowing solid foods which seemed to stick at the back of the throat. She lost two stone (12·7 kg.) in weight and became dyspnoeic on the slightest exertion. To direct questioning she stated that 12 months ago her hands had become swollen, which she attributed to handling *Primula japonica*. She had some trouble in writing on the blackboard at that time but the swelling soon subsided with resulting improvement in function. She felt, however, that her fingers had never quite recovered their former dexterity. At no time had she experienced any pain and did not complain of any symptoms referable to the skin.

On examination she was seen to be a frail, white-haired old lady. The optic fundi and pupils were normal. Neither eye could be fully abducted, the right falling short of the outer canthus by 2 mm. and the left by 4 mm., but there was no diplopia. There was slight ptosis of the right eyelid. Sensation on the face was normal and there was no obvious weakness of the facial or masticatory muscles. Her voice was weak and nasal and her cough was extremely weak and ineffective, but the palate and tongue appeared to move normally. The extensor muscles of the neck were weak out of all proportion to her general muscular state. The muscles of the limbs were generally feeble but there was no localized weakness or wasting. There were slight contractures of the flexors of the fingers. The tendon reflexes were all present, the plantars were flexor and there was no sensory loss.

The skin appeared normal except over the hands and wrists. There was some cracking and flaking on the flexor surfaces of the fingers and the skin of the lower forearms seemed somewhat thicker than normal, but there was no erythema. The ankles were oedematous and pitted easily.

There was dullness to percussion at the base of the right lung and the patient became breathless after taking a few steps. The liver and spleen were not palpable and the heart was clinically normal. While under observation she was afebrile.

A blood count showed no abnormality and the erythrocyte sedimentation rate (E.S.R.) was 4 mm. in the first hour (Wintrobe). The blood Wassermann reaction was negative. The basal metabolic rate was increased by 15%. The serum globulin was not raised. A radiograph of the chest showed appearances thought to be those of encysted fluid at the base of the right lung. On screening the upper oesophagus was seen to contain air in the resting state and was quite inert on swallowing. Barium passed through readily in the upright position but not with the patient supine.

The subcutaneous injection of 1·5 mg. of neostigmine was without effect on the patient's weakness. A diagnosis

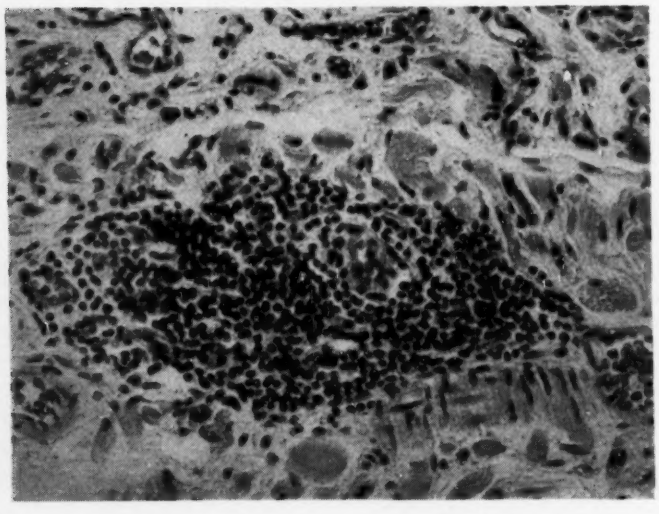
of dermatomyositis was made, but before further investigation or treatment could be carried out the patient died suddenly of respiratory failure on February 24, 1951.

A post-mortem examination was performed (J. C. B.). The voluntary muscles of the limbs, face, and thoracic and abdominal walls were atrophic, pale, and gelatinous, notably the temporal muscles. The axillary lymph nodes were soft and moderately enlarged. There were thick, fibrous adhesions at the right lung base and there was a grey, fleshy nodule 2 cm. in diameter in the right lateral lobe of the thyroid. No significant abnormality was seen in the other organs. No thymic tissue was seen in the mediastinal fat.

Microscopic Findings.—All sections were stained with haematoxylin and eosin and by the periodic-acid-Schiff technique of McManus (1946) and Hotchkiss (1948) for connective tissue. The muscles examined were the temporal, and the extensors of the forearm, upper oesophagus, diaphragm, and psoas major. All showed oedema with focal lymphocytic and histiocytic infiltration, which was often perivascular. There was atrophy and hyaline degeneration of the muscle fibres and commencing interstitial fibrosis. The muscles of the forearm and oesophagus were only slightly affected, but in the sections of the diaphragm, temporal, and psoas muscles hardly a single healthy muscle bundle was seen (Fig. 1). Despite careful search no evidence of vascular disease was found. Sections of skin from the forearm showed senile elastosis only and the mucosa of the upper oesophagus was normal.

The axillary lymph nodes showed a mild reactive hyperplasia. The right lung base was fibrotic with some mild, non-specific inflammation. The bone marrow appeared normal. The nodule in the thyroid proved to be an early round cell carcinoma but the remainder of the thyroid tissue appeared normal. A microscopic chromophobe adenoma was found in the pituitary. Sections of the spleen, liver, and adrenal, kidney, and pancreas showed no obvious abnormality. No thymic tissue was found on microscopy.

FIG. 1.—Section from diaphragm in Case 1. The muscle bundles are extensively damaged and there is a collection of lymphocytes round a healthy blood vessel. H. and E. × 150.



Important points in the diagnosis were the previous history of swelling of the hands and the slight changes in the skin. The clinical picture otherwise bore a strong resemblance to myasthenia gravis. Some form of thyrotoxic myopathy might be considered in view of the thyroid nodule and of the basal metabolic rate at the upper limit of normal, but is extremely improbable as the carcinomatous cells were undifferentiated and unlikely to show hormonal activity. The pathological changes in the muscles, while extremely striking, cannot be regarded as entirely specific for dermatomyositis.

Case 2 : G. C. (237315).—A woman aged 49 was admitted to the Manchester Royal Infirmary under Dr. F. R. Ferguson in February, 1952, complaining of weakness of the legs and difficulty in swallowing. In November, 1950, she had had a febrile illness lasting a few days with symptoms of malaise and fatigue. These symptoms rapidly passed off, but afterwards she began to notice slowly increasing weakness of the legs, which was especially marked on climbing stairs or on rising from a chair. Eventually the weakness caused great restriction of her activity and she no longer went outside her own house. She thought that her arms were not quite as strong as formerly, but this was only apparent on attempting to lift heavy weights. In May, 1951, she began to have difficulty in swallowing solid foods which seemed to stick high up in the throat. At this point she was admitted to another hospital where oesophagoscopy was performed without any lesion being found. It was noted that the eyelids were drooping and that the right side of the face was weak and a diagnosis of myasthenia gravis was made, although there was no response to a test dose of neostigmine. The dysphagia, however, began slowly to improve and by the time she was admitted to the Royal Infirmary she was having little difficulty in swallowing solids, but had noticed that fluids would often regurgitate down her nose. She thought that she could not chew her food as well as formerly and that her voice had become weaker.

On further enquiry she said that two years ago her left ankle had become swollen, but as it was painless she had paid little attention to it. A month before her admission she sustained a minor injury to her right shin and following this her right ankle had also become swollen. For the past year her hands had been liable to go blue in cold weather but had never been swollen. The entire course of her illness had been painless and the most pressing enquiry could not elicit any symptoms referable to the skin. The patient's past health had been good and her last menstrual period had been two years before.

On examination the patient was stout and did not appear ill. There was no abnormality of the optic fundi, pupils, or ocular movements but there was striking bilateral ptosis (Fig. 2). There was no sensory loss on

FIG. 2.—Case 2 showing bilateral ptosis.

the face and no detectable weakness of the jaw. The right side of the face moved less well than the left. The palate was somewhat pale and oedematous and the right side did not move.

There was no detectable weakness or wasting of the arms but the right biceps and both triceps jerks were absent. There was considerable symmetrical weakness of the muscles of the pelvic girdle, particularly the psoas muscles and glutei. The patient was obese and no wasting could be seen. The consistency of the muscles was not altered neither was there any undue muscle tenderness. The quadriceps muscles were not noticeably weak but the knee jerks were diminished compared with the ankle jerks. The patient walked with the waddling gait of a proximal myopathy and she had great difficulty in rising from a chair. No sensory loss was found and the plantar reflexes were flexor.

The skin over the forehead and cheeks was shiny and somewhat thickened, particularly on the right cheek, and there was some scaling on the forehead. The face and neck would frequently flush in a variable mottled pattern but there was no fixed erythema. The skin around the eyes was of a faintly violaceous hue. These skin changes were only obvious on close inspection and had, indeed, never been noticed by the patient. The skin of the hands was normal. Both feet and ankles were swollen but the appearance of the skin was normal. The swelling was firm and could only be pitted with difficulty and the skin was firmly adherent to the underlying oedematous tissues. The liver and spleen could not be felt and she was afebrile.

A blood count did not show any abnormality but the E.S.R. was 53 mm. in the first hour (Wintrobe). The serum proteins were normal. The cerebrospinal fluid was normal and the Wassermann reaction negative. The urine contained 1,092 mg. of creatinine and 239 mg. of creatine per 24 hours on a single estimation. A barium swallow showed no constant narrowing of the oesophagus and only a little irregularity of outline. A biopsy taken from the right quadriceps, a muscle not noticeably weak but of easy access, showed no definite abnormality.

She was given 100 mg. of adrenocorticotrophic hormone (A.C.T.H.) daily for 10 days. Despite a good eosinopenic response the only change in the clinical condition was a reduction in the violaceous hue of the periorbital skin. The E.S.R. did not fall and there was no significant change in the excretion of creatinine or creatine. In view of the absence of any dramatic change and of the lack of adequate supplies of A.C.T.H. treatment was not further prolonged.

This case had previously been diagnosed as myasthenia gravis. Important points in the history which were not stressed by the patient were the swelling of the ankles and the onset of Raynaud's syndrome. The slight changes in the skin and the oedematous appearance of the palate were significant points in the examination. The negative biopsy from a muscle not grossly weakened in no way affects the diagnosis (Jager and Grossman, 1944).

Case 3 : J. B. (168686).—A girl aged 14 was admitted to the Manchester Royal Infirmary under Dr. F. R. Ferguson on September 1, 1950. She had been born after a normal delivery but her head had been held on one side since birth. Information about her early life was scanty as her mother had died of pulmonary tuberculosis shortly after the child was born. She walked at the age of 2 and did not talk well until she was 4. She attended school but was thought to be backward. At the age of 10 a left sternomastoid tenotomy was done for congenital torticollis with good result, but at about this time the child seemed to stop growing and became progressively weaker and thinner. It was noticed that she had particular difficulty in climbing stairs. This weakness had followed a fluctuating course and had been particularly severe after she had spent three weeks in bed in another hospital. About a year after the onset of the muscular weakness she developed soreness and irritation on the knuckles and later on the face. This skin condition had persisted and had gradually become worse.

The patient had no full-blood siblings, but her stepsister, aged 9, was normal and was already bigger than the patient. No similar disease was known in preceding generations.

On examination the child was small and underdeveloped, being 4 ft. (122 cm.) high and weighing only 3 st. (19·1 kg.). There was no mammary development or growth of body hair and she had not menstruated. There was no gross weakness of any muscles supplied by the cranial nerves but the limb musculature was severely and uniformly wasted (Fig. 3). Weakness of the limbs was most marked proximally especially in the legs, leading to great difficulty in climbing stairs and to inability to rise from a supine position. The muscles were not tender but were unduly firm and there were flexion contractures of the elbows and knees. The tendon reflexes were all absent. There was no sensory loss and the plantar reflexes were flexor.

FIG. 3.—Case 3 showing wasting and contractures.

The skin of the face was shiny and atrophic with erythema and slight oedema around the eyes and some

scaling on the forehead. Over the extensor surfaces of the joints of the upper limbs the skin was atrophic and telangiectatic. On the backs of the thighs there was some faint reticulated pigmentation. The liver and spleen could not be felt and the patient was afebrile.

A blood count showed a mild normochromic anaemia but no other abnormality. The E.S.R. was 43 mm. in the first hour (Wintrobe). The serum proteins, calcium, and phosphorus were within normal limits and a fat balance showed 99% absorption. Estimation of urinary hormones (Miss B. M. Hain) showed 3·1 mg. of 17-ketosteroids and 3–4 mouse units of follicle-stimulating hormone per 24 hours, both values distinctly low for her age. Radiography of the bones showed considerable osteoporosis but normal ossification and dentition for her age. Extensive subcutaneous calcinosis was present (Fig. 4) but no renal calcification.

FIG. 4.—Case 3 showing calcinosis.

A biopsy was taken from the right quadriceps. At operation the texture of the skin and of the thin layer of subcutaneous fat appeared normal, but the deep fascia was extremely thick and blended with the underlying pale avascular muscle to form a rigid mass with a gritty feeling to the finger, presumably due to deposits of calcium. Microscopic examination of the fragment removed showed no abnormality of the skin or superficial fat, but extensive calcinosis was present in the deeper fat. The fascia showed slow necrobiosis of the collagenous fibrous tissue and no evidence of an inflammatory reaction was seen. No tissue recognizable as muscle was found in the specimen.

The patient was last seen in December, 1951, when there had been no substantial change in her condition.

Although the cutaneous lesions were much more obvious than in Cases 1 and 2 the correct diagnosis was not established until some four years after the onset, Still's disease and progressive muscular dystrophy being suggested at different stages of the disease. The case is presented as showing the extreme degree of muscular atrophy that can occur in the later stages of chronic dermatomyositis. The infantilism was presumably similar to that seen in other severe chronic diseases in childhood.

Discussion

The number of reported cases of dermatomyositis is now very large and it is no longer practicable to attempt a comprehensive review. The difficulty of such a task is increased by the unresolved controversy on the specificity of dermatomyositis as a disease and on its possible identity with a group of other conditions including scleroderma and disseminated lupus erythematosus. This problem has been fully reviewed by Banks (1941) and it seems that, while there is clearly an overlap with other "collagen diseases", dermatomyositis retains sufficient individuality to warrant description as a clinical entity.

Onset.—Dermatomyositis is an acute, subacute, or chronic condition of unknown cause affecting both sexes and beginning at any age, even in infancy (Kinney and Maher, 1940), but commonest between the ages of 10 and 50. The presenting symptoms, which may be preceded by vague prodromata of ill health or by an acute infection, are extremely variable and may be referable to the skin or to the muscles. Steiner (1905) noted that pain in the muscles usually preceded the appearance of a rash, and O'Leary and Waisman (1940) in a review of 40 cases, found that muscular symptoms, either pain or weakness, occurred first in 18 patients. Of Sheard's (1951) 25 cases, muscular fatigue or weakness was the presenting symptom in five, muscular pain in five, and oedema or a rash in 15. As it is those cases in which muscular weakness is the presenting symptom that are likely to be seen by a neurologist it is important to realize that the interval between the onset of muscular and cutaneous symptoms may be as long as several years (Jager and Grossman, 1944, Case 1). Complaints of dysphagia, dyspnoea, and weakness of the voice may occur early in the disease and accompany those of weakness of the limbs. The onset of Raynaud's syndrome is a not uncommon presenting symptom (Lewis, 1940 ; Dowling, 1940).

Muscular Involvement.—The involvement of the muscles may become widespread, leading to almost complete paralysis of the limbs and trunk (Friedman, 1926), but in less severe cases the weakness of the limbs is often proximal in distribution (Oppenheim, 1911 ; Barker, 1930) as in Case 2 in the present series. Muscles supplied by the cranial nerves are

often affected, and diplopia due to weakness of the ocular muscles (O'Leary and Waisman, 1940), nystagmus (Marinesco, Draganesco, and Façon, 1931), ptosis (Kinney and Maher, 1940), facial weakness (O'Leary and Waisman, 1940), weakness of the jaw and tongue (Marinesco and others, 1931), palate (Stuckey, 1935), and neck muscles (Weber and Bode, 1932) have all been reported. Dysphagia is a common symptom occurring in 27 of O'Leary and Waisman's (1940) 40 cases. A weak and nasal voice is often encountered (Carney, 1927) and weakness of the respiratory muscles frequently causes dyspnoea (Kinney and Maher, 1940). According to O'Leary (1949a) the sphincters may be involved. Muscular pain is a common complaint at some stage of the disease but may be absent in the more chronic cases. The muscles are often tender, sometimes to an agonizing degree (Keil, 1940), and muscular oedema is common during acute exacerbations. At this stage the consistency of the muscles may be soft and doughy, while in a later stage they may be unduly hard and no longer tender (Witts, 1936). Atrophy may develop late in the disease and, in addition to the limbs, may involve the tongue (Stuckey, 1935), the masseters (Kinney and Maher, 1940), and sternomastoids (Keil, 1940). When selective the atrophy is usually proximal in distribution but may be distal, and contractures may occur as in Cases 1 and 3 in the present series.

Cutaneous Involvement.—The cutaneous lesions will not be discussed in any detail except to say that they are entirely non-specific and may vary from an erythematous macular rash to frank scleroderma. In the present context it is important to note that such lesions may be insignificant or even entirely absent throughout the course of the disease (Steiner, 1905; O'Leary and Waisman, 1940; Sheard, 1951). In other cases they may only occur at certain stages of the disease and may no longer be present when the patient is first seen (Carney, 1927). Nixon (1907) recognized that the muscles might be disproportionately involved and Wilson (1940) also commented on this. Subcutaneous oedema is a very frequent sign and is particularly common in the periorbital tissues. Again the oedema may be present only fleetingly as in the present Case 1.

Systemic Involvement.—Dermatomyositis is not a purely local disease of the skin and muscles, and signs of more widespread lesions may be present. The spleen (Witts, 1936; Ragan, 1950) or liver (Kinney and Maher, 1940) may be enlarged and more rarely there is a generalized lymphadenopathy (de Graciansky, 1949). Articular swelling is another occasional finding. Bruce (1938) reported retinal haemorrhages and exudates in three cases. Fever is common in the acute stages but is far from constant.

Laboratory Diagnosis.—Laboratory aids to diagnosis are sometimes helpful but seldom diagnostic. Schuermann (1939) reviewed the haematological findings which include eosinophilia in less than half the reported cases, and a frequently raised E.S.R. The serum globulin is sometimes markedly increased (Ragan, 1950). As might be expected creatinuria is constantly present (Griffiths, 1940) but the disturbance of carbohydrate metabolism reported by the same author could not be confirmed by Jager and Grossman (1944).

Skin and muscle have frequently been removed at biopsy in an attempt to establish the diagnosis. The findings in the skin are not diagnostic and will not be further discussed. The changes in the muscles have frequently been described but O'Leary (1949b) stated that it had not been possible to recognize a classical histological picture in dermatomyositis. The changes reported in varying degree by many authors consist essentially of atrophy and fragmentation of muscle fibres with an apparent increase in sarcolemma nuclei; infiltration with lymphocytes, often perivascular; and an increase in interstitial tissue. Dowling (1940) emphasized the lack of specificity of these changes and considered that they closely resembled those found in myasthenia gravis, thyrotoxicosis, and in the myopathy described by Nevin (1936), and Madden (1950) has described similar changes in disseminated lupus erythematosus.

Prognosis.—In most series the mortality is between 50 and 60%, and according to Sheard (1951) the prognosis is worst in acute cases in young adults. Complete recovery is possible but prognosis must be guarded as remissions and exacerbations are commonly reported. Even in apparently "burnt out" cases with severe sclerotic lesions of the muscles there may be some smouldering activity as suggested by the raised E.S.R. in the present Case 3.

Differential Diagnosis.—It is evident that dermatomyositis can present a formidable problem in differential diagnosis. From a neurological point of view most cases fall into one of three groups each with its own diagnostic difficulties. In the first group, of which there is no example in the present series, there is a rapid onset of proximal

weakness of the limbs with spontaneous pain and increased muscle tenderness and often loss of tendon reflexes. The resemblance to polyneuritis can be striking and cases have been erroneously so diagnosed (Rosenthal and Hoffmann, 1923 ; Keil, 1940). The presence of florid skin lesions and of subcutaneous and muscular oedema usually clarifies the diagnosis, but it is possible that the peripheral nerves may in fact be occasionally involved in dermatomyositis. Senator (1888, 1889, 1893) diagnosed the condition of " neuromyositis " on the grounds of changes in the nerves and muscles at necropsy, but he could find little clinical evidence of neural involvement beyond tenderness of the nerve trunks and slight sensory changes in one case. Adler (1894) and Levy-Dorn (1895) diagnosed the same combination in their cases. Rosenthal and Hoffmann (1923) considered that loss of tendon reflexes and tenderness of the nerves in their case justified a diagnosis of " dermatoneuromyositis " and Kinney and Maher (1940) also reported demyelination of peripheral nerves. Loss of tendon reflexes, which is of frequent occurrence in dermatomyositis, is not, of course, conclusive evidence of nervous disease, and Oppenheim (1911) stated that reflexes were lost as the particular muscles became involved. Unequivocal signs of disease of the peripheral nerves must be extremely rare but their occasional occurrence may certainly add to the diagnostic difficulties.

In the second group, of which Cases 1 and 2 are examples, there is a more gradual onset of weakness of the limbs accompanied by symptoms suggestive of a bulbar palsy. As has already been emphasized, muscular pain, swelling, or tenderness may be transient or absent and cutaneous lesions may be insignificant. Muscular wasting may suggest a diagnosis of progressive muscular atrophy (Collier and Wilson, 1913 ; Keil, 1940) but the most important source of possible confusion is with myasthenia gravis. Weber and Bode (1932) presented a case of scleroderma combined with myasthenia gravis, a diagnosis which Weber (1938) subsequently amended. In many cases the initial complaint is of easy fatiguability rather than of permanent weakness and the remittant nature of certain symptoms, as with the dysphagia in Case 2, is another point of similarity with myasthenia gravis. How difficult the distinction may be can be seen from the case of Ragan (1950) in which there appeared to be some response to neostigmine.

In the third group, of which Case 3 is an example, dermatomyositis may simulate other muscular diseases to some degree. Keil (1940) stated that he had known of cases diagnosed as progressive muscular dystrophy but the resemblance can seldom be close. A more probable source of error is the menopausal myopathy of Shy and McEachern (1951a). Before the onset of dysphagia in Case 2 the proximal weakness of the legs in a woman of menopausal age would strongly have suggested this diagnosis. The late myopathy of Nevin (1936) must also be distinguished. The condition of generalized myositis fibrosa (Burton, Cowan, and Miller, 1923 ; Blau, 1938) is probably not a distinct entity. Skin lesions very similar to those of Case 3 were present in both of Blau's cases, and Keil (1940) stated that he had examined one of these patients and considered the diagnosis to be dermatomyositis. In Burton and his colleagues' case transient oedema of the eyelids occurred early in the course of the disease. Calcinosis universalis is also probably a sequel to dermatomyositis in most cases and not a separate entity (Hecht, 1940 ; Nørregaard, 1948).

Treatment.—The correct diagnosis of dermatomyositis is of some practical importance as there have been recent claims of successful treatment. Zarafonetis, Curtis, and Gulick (1950) obtained a good response in one case with para-aminobenzoic acid, and there have been several claims of success with A.C.T.H. (Oppel, Coker, and Milhorat, 1950 ; Elkinton, Hunt, Godfrey, McCrory, Rogerson, and Stokes, 1949). Such treatment is not without danger, however, as Ragan (1950) reported an increase in weakness. Shy and McEachern (1951b) have obtained good results with cortisone, especially in acute cases. In assessing the results of treatment the remittant nature of the disease must be remembered, but there seems no doubt that the unknown disease process responsible for the clinical syndrome of dermatomyositis can be influenced by modern methods of treatment.

Summary

A description is given of three patients with dermatomyositis in whom at one stage alternative diagnoses of muscular or nervous disease were considered. The necropsy findings are given in one case.

The relevant literature is reviewed and it is emphasized that dermatomyositis may present as a variety of syndromes of muscular dysfunction and that the condition must be considered in the differential diagnosis of bulbar palsy, peripheral neuropathy, and the myopathies.

We are grateful to Dr. F. R. Ferguson for permission to report on his patients, and to Professor A. C. P.

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BOOK REVIEWS

Die Zerebrale Angiographie. By H. Krayenbühl and H. R. Richter. (Pp. 213 ; 100 illustrations. DM. 59.70). Stuttgart : Georg Thieme. 1952.

In this book Professor Krayenbühl and Dr. Richter have produced an excellent monograph. After 60 pages of text, which contain some good diagrams and *x*-ray illustrations on general points, the rest of the work is devoted to an illustrative atlas of cerebral angiography. Here most of the conditions are exemplified in which this procedure is of diagnostic value. Not only are *x*-ray photographs of exceptional clarity reproduced, but the main diagnostic points are further emphasized in accompanying line diagrams. This book will prove of value to all those interested in neurological science ; nor need those whose command of German is very limited feel excluded, for the arrangement is such that they can still readily use it as a work of reference. However, the neophyte in the practice of angiography should perhaps be warned that both the actual intra-arterial injection and the *x*-ray procedure require both attention to the smallest details and considerable practice before results such as are here illustrated can be hoped for. On the wider view, it is perhaps a small lacuna in this book that such brief mention is made of the method of rapid serial angiography.

A History of Neurological Surgery. Edited by A. Earl Walker. (Pp. xii + 583 ; 152 figures. 91*s.* 6*d.* net.) London : Ballière, Tindall and Cox. 1951.

Two years ago the members of the Division of Neurological Surgery, the Johns Hopkins University, wrote a series of essays tracing the development of neurological surgery. These have now been collected into one volume under the general editorship of Professor Earl Walker. Neurosurgeons are indebted to this team for its enterprise and energy. The extensive bibliography of 2,371 entries ranges over the world literature and is evidence of the thoroughness with which the authors have undertaken their task.

Each essay has for its subject the development of some particular aspect of neurosurgery, such as " Diagnostic Procedures ", and " Surgery of the Hypophysis ", and the accompanying historical illustrations are clear and well chosen. In addition to the main essays, there are bibliographical sketches of neurosurgeons who have made major contributions to the subject or to the development of the speciality in their own country. These, together with other short annotations, have been interspersed between the essays, an arrangement which is not altogether a happy one, as it detracts from the main text. In future editions they might well be grouped together at the end of the volume.

The price of the book should not discourage those interested in the subject from possessing a valuable reference book and one which provides such an interesting commentary on the development of this speciality.

Pratique Neurologique. By M. Riser. Vols. I and II. (Pp. 1,428 ; 374 illustrations. Fr. Frs. 10,000.) Paris : Masson & Cie. 1952.

Advances in neurology by way of its ancillary sciences have been considerable of late. Until this new knowledge is sifted and integrated, a neurological text to be satisfactory must either treat the subject exhaustively in a series of volumes or give an outline with adequate references to the wider literature, or else approach it by way of special monographs. This book, in two volumes and some 1,400 pages, falls somewhat between these three stools.

The viewpoint is purely clinical, so that no space is wasted on the elementary anatomy and physiology of many textbooks. The arrangement is symptomatological. Thus all paralyses are grouped together, followed by other abnormalities of movement ; and disorders of consciousness and perception include sections on deafness, visual lesions, and agnosia and aphasia. This seems less satisfactory than the usual method of grouping according to anatomy or pathology.

An entirely clinical approach has certain advantages, but the subject is left hanging in mid-air unless an attempt is made to integrate it with advances in neurophysiology. This the present book hardly does, nor does it make any but scanty references to treatment, a surprising lacuna in a " practice of neurology ". It follows the Salpetriere tradition of careful clinical description, and thereby corrects the tendency to overemphasize the value of experimental findings. However, there are now fields of thought and investigation outside the clinic but essential to clinical neurology, which receive little recognition here. The criticism is perhaps one of a specific point of view. The book will, nevertheless, be of interest and value to English and American readers, especially to those who are prejudiced by dissimilar traditions.

Fundamentals of Neurology. By Ernest Gardner. 2nd edition. (Pp. 336 plus index ; illustrated. 24*s.*) London : W. B. Saunders. 1952.

This book provides an excellent introduction for the student of neurology. It is clearly written, and presents the subject in such a way as to arouse the student's ambition to learn more by referring to the selected references provided with each chapter.

Useful additions to the text are a glossary of neurological terms, and short descriptions of those whose names are famous in neurology.

Lehrbuch der Nervenkrankheiten. By Robert Bing. 9th edition. (Pp. 818. 60 Sw. Fr.) Basle : Benno Schwabe & Co. 1952.

After looking through this book one must conclude with regret that famous textbooks of neurology, which first appeared early in this century, are not now suitable for the publication of new editions without the most drastic alterations. In this, the ninth edition of a well known textbook, there is, as in previous editions, a wonderful collection of clinical facts, but this is not now enough, for the modern student of neurology must correlate clinical facts with the latest anatomical and physiological knowledge, and here this textbook, like many others, is far out of date.

Perhaps the most disturbing feature, however, is a failure to cut out " dead wood " in the sections on treatment. Neurology is no longer only a diagnostic exercise, and the planning of the proper treatment of, say, severe myasthenia gravis, meningitis, bulbar poliomyelitis, post-exathmatous encephalomyelopathy, or cerebral abscess, makes exacting demands on all concerned, and requires a sense of urgency and attention to detail which is not to be learned from the pages of this book. Further, the really effective drugs are concealed in an astonishing list of long-since discarded remedies, so that only the expert can unravel the tangle. Although, for example, the treatment of meningitis with sulphonamides and antibiotics is referred to briefly, the reader is horrified to find on p. 392 a description of treatment by the long-discarded and dangerous intrathecal antiserum.

Psychosurgical Problems. Edited by Fred A. Mettler. (Pp. 357 ; 57 tables, 56 figures and 4 plates. 42*s*.) London : Routledge & Kegan Paul. 1952.

This is a record of the second research project undertaken by the team known as the Columbia Greystone Associates. Substantially, it is a compendious account by 36 contributors of pre-operative and post-operative observations on 25 patients suffering from schizophrenia of at least three years' duration subjected to various cerebral operations. These operations, which are succinctly described, were : in 12 cases, ligation of the superior cerebral (cortical-dural) veins ; in two cases, thermocoagulation of areas 9 and 10 ; in nine cases, transorbital lobotomy ; and in two cases, thalamotomy. There were six control subjects.

Each patient was scrutinized by general physicians, neurologists, psychologists, and psychiatrists, with appropriate ancillaries, and the bulk of the book consists of extremely detailed records of the findings in these disciplines before and after operation.

The results are inconclusive so far as the therapeutic effects of the operations are concerned, but the work provides a useful record of the changes that occurred, or did not occur, in physiological and psychological functions, as a result of the operations that were done. There is a clear exposition of the practical difficulties of organizing a research project of this kind, and of obtaining reasonably well standardized clinical material, even from the population of a very large mental hospital.

The last chapter in the book is devoted to a follow-up account of the patients who were the subject of the first Columbia Greystone research project two years after operation.

The bibliography is comprehensive and the index adequate.

Le Syndrome de Morgagni-Morel. By André Calame. (Pp. 154 ; 27 figures. Fr. Frs. 700.) Paris : Masson & Cie. 1951.

This book reviews at length the literature on hyperostosis frontalis interna (H.F.I.) and the syndrome of Morgagni-Morel, H.F.I., adiposity, virilism, and various neuropsychological disorders, and the author adds 60 new cases of H.F.I., some studied at necropsy, others diagnosed during life. From the gross appearances and microscopic study he concludes that the hyperostosis grows solely from the inner table of the skull and may immure fragments of the dura mater as it grows. He attributes the localization of the hyperostosis to a number of anatomical peculiarities of the frontal region of which one of the most important is the fact that it receives its blood supply not from the external carotid artery, but via the ethmoidal artery from the internal carotid artery. He has studied the pituitary microscopically and has found little abnormal except a tendency to diffuse basophilism.

These pathological studies are interesting and fully described, but they occupy a relatively small part of the book ; the remainder is largely concerned with clinical reports, and includes some very hypothetical statements which do not appear to be supported by the facts given. Of those who agree with Sneeburg that " H.F.I. is a not uncommon incidental skull thickening in women that is unrelated to whatever clinical state may accompany it ", few will be converted by this book. And of those who believe that the syndrome is a real one, few will believe in the author's hypothesis that it is due to a primary lesion of the adrenal cortex affecting the pituitary by causing raised intracranial tension.

In brief this book reports some interesting pathological observations mingled with uncritical assumption and theorizing.

Hemifacial Spasm. By Robert Wartenburg. (Pp. 86 ; 27 illustrations. $4.00.) New York : Oxford University Press. 1952.

This small book records the author's views on the mechanism of hemifacial spasm. These are not always easy to follow. The associated movements seen after regeneration in Bell's palsy are described and are sometimes followed by the development of facial spasm, but the author does not accept the usual view that faulty direction or axonal branching is the cause of mass movements in the muscles supplied by the facial nerve. This is puzzling, for a regenerating nerve always leads to

mass movement, and experimental observations have correlated this with axonal branching. The author considers that facial spasm is a release phenomenon at the nuclear level, but he presents little new evidence either as regards clinical signs or treatment.

Les Nerfs Craniens. By Rene-Marcel de Ribet. (Pp. 517. Fr. Frs. 3,500.–). Paris : G. Doin. 1952.

This book of 517 pages (with an appendix of some 50 pages with schematic diagrams of the spinal peripheral nerves and nerve roots) deals only with the anatomy of the 12 cranial nerves, and even so mentions their intracerebral course, connexions, and nuclei only very briefly. It should therefore give this restricted field fairly intensive treatment. It will certainly have some value as a reference book, but from the clinician's point of view it is too schematic and there are too few illustrations as opposed to diagrams ; even in the latter the relations of the cranial nerves, and especially their vascular relations, always important for the neurologist, are sometimes not well shown. Indeed, the many diagrams, by which the book would presumably wish to be judged, are of very uneven value, some tending to obscure rather than clarify the points they wish to illustrate.

Gehirnschnitt Modell. By Eduard Weber. 2nd ed. (18 figures. DM. 4.20.) Munich : Urban and Schwarzenberg.

After spending five painstaking hours assembling this model, the reviewer is loath to pull it to pieces too harshly, either physically or verbally. It is a pity that the final product—in fact a masterpiece of detailed planning—looks both flimsy and disorderly.

To gain true benefit from the model, it is necessary to assemble it oneself, as some of the deeper anatomy is of necessity hidden or replaced when the outer portions are added. Moreover, as the model is made of sheets of flat cardboard (already painted, labelled, and partly cut out) some of the nuclei, especially the thalamus and lentiform nucleus, assume a rather curious appearance when seen from certain angles in the finished arrangement. However, it is doubtful whether those who are not already familiar with the anatomy of the brain (or alternatively have a good command of German and are endowed with spatial constructive ability) would get very far with it.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Die Scopolaminwirkung. Vergleichend psycho- pathologisch-elektroencephalographische Untersuchung. By Hans Heimann. (Pp. 80 ; 24 illustrations. Sw.fr. 12.50.) Basle : S. Karger Ltd. 1952.

Muscle Relaxation as an Aid to Psychotherapy. By Gerald Garmany. (Pp. 65. 5*s*. 6*d*.) London : The Actinic Press Ltd. 1952.

Die Alkoholhalluzinosen. By G. Benedetti. (Pp. 58 ; 17 tables. DM. 7.50.) Stuttgart : Georg Thieme. 1952.

Klinische und sprachwissenschaftliche Untersuchungen zum Agrammatismus. By Fr. Panse, G. Kandler, and A. Leischner. (Pp. 72. DM. 6.00.) Stuttgart : Georg Thieme. 1952.

Die Neurose als Reifungsproblem. By Wolfgang Kretschner, Jr. (Pp. 93 ; 3 tables. DM. 10.80.) Stuttgart : Georg Thieme. 1952.

Poliomyelitis. By W. Ritchie Russell. (Pp. VII + 84 ; 20 figures ; 5 tables. 14*s*.) London : Edward Arnold. 1952.

A Further Study of Visual Perception. By M. D. Vernon. (Pp. 289 ; 30 figures. 35*s*.) London : Cambridge University Press. 1952.

Psychosomatic Medicine. By Franz Alexander. (Pp. 300 ; 5 figures. 21*s*.) London : George Allen and Unwin. 1952.

The Biology of Mental Health and Disease. The twenty-seventh annual conference of the Milbank Memorial Fund. 108 contributors. Foreword by Stanley Cobb. (Pp. XXV + 624 and index ; 213 figures ; 58 tables. 75*s*.) London : Cassel and Co. 1952.

Die körperlichen Behandlungsverfahren in der Psychiatrie. Band I : Die Insulinbehandlung. By Max Müller. (Pp. 295 ; 4 illustrations ; 20 tables. DM. 36.00.) Stuttgart : Georg Thieme. 1952.

Einführung in die Enzephalographie (Pneumenzephalographie). 2nd revised edition. By Otto Schiersmann. (Pp. 135 ; 186 illustrations. DM. 36.00.) Stuttgart : Georg Thieme. 1952.

Office Psychiatry. The Management of the Emotionally and Mentally Disturbed Patient. By Louis G. Moench. (Pp. 300 and index ; 81 figures. 45*s*.) Chicago : Year Book Publishers, Inc. 1952.

Transactions of the Ophthalmological Society of the United Kingdom. Vol. LXXII, Session 1952. (Pp. 731 and index ; 260 figures ; tables. No price.) London : J. and A. Churchill. 1952.